A STUDY OF
PULMONARY MANIFESTATIONS IN
RHEUMATOID ARTHRITIS

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause. Although there are a variety of systemic manifestations, the characteristic feature of established RA is persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The potential of the synovial inflammation to cause cartilage damage and bone erosions and subsequent changes in joint integrity is the hallmark of the disease. Despite its destructive potential, the course of RA can be quite variable. Some patients may experience only a mild oligoarticular illness of brief duration with minimal joint damage, but most will have a relentless progressive polyarthritis with marked functional impairment.[2]

Though it is considered a disease predominantly involving the joints it can cause a variety of extraarticular manifestations. It can affect skin, eye, cardiovascular, hematological, respiratory, and nervous systems independent of the immunosuppressive drugs. Pulmonary involvement is one of the important extraarticular features of RA and occurs in the form of pleural diseases, pulmonary nodule, interstitial lung diseases, airway diseases, and pulmonary vascular disease apart from drug induced lung injury.

REVIEW OF LITERATURE

HISTORICAL REVIEW

Historical review revealed that Hippocrates and other Greek and Roman writers gave possible descriptions of the disease (Short, 1974). There are suggestive descriptions in the Sanskrit writings of Charaka Samhitha of 100 AD (Sturrack et al. 1977) and by the 17th century English physician, Thomas Sydenham (Short, 1974).

Sydenham described the disease state which he called "Rheumatoid Polyarthritis". But it was clearly described by Landre Beauvais (1800). Garrod (1959) used the term: "Rheumatoid Arthritis" and the clinical description of the disease entity began to emerge. The modern concept of the disease evolved by the pain-staking work of Nicolas and Richardson (1906), Jones, Millard Smith (1930), Lewis Faning, Short, Bauer and Reynold (1957). Short's text book (1957) set the stage for the modern era of investigations and inquiry in the field of Clinical Rheumatology. American Rheumatism Association carefully drafted the description and the criteria for the diagnosis of Rheumatoid Arthritis.

DEFINITION

Rheumatoid Arthritis is a chronic, symmetrical, inflammatory, deforming polyarthritis affecting small and large peripheral joints with associated systemic disturbances such as vasculitis and nodules. Characteristically the course of the disease is prolonged with exacerbations and remissions.[5]

GENERAL ASPECTS OF RHEUMATOID ARTHRITIS

EPIDEMIOLOGY

The prevalence of RA is ~0.8% of the population (range 0.3–2.1%) [26]; women are affected approximately three times more often than men[27]. The prevalence increases with age, and sex differences diminish in the older age group. RA is seen throughout the world and affects all races. The onset is most frequent during the fourth and fifth decades of life, with 80% of all patients developing the disease between the ages of 35 and 50. The incidence of RA is more than six times greater in 60- to 64-year-old women compared to 18- to 29-year-old women. Recent data indicate that the incidence of RA may be diminishing. Moreover, disease severity appears to be declining, although it is uncertain whether this reflects more aggressive therapeutic interventions.[2]

AETIOLOGY

Rheumatoid Arthritis is a disease determined by genetic and environmental factors, namely an infectious agent which is systemically distributed in patients, but has a particular predilection for synovial joints.

GENETIC FACTORS

Family studies indicate a genetic predisposition. Severe RA is found at approximately four times the expected rate in first-degree

relatives of individuals with disease associated with the presence of the autoantibody, rheumatoid factor; 10% of patients with RA will have an affected first-degree relative. Moreover, monozygotic twins are at least four times more likely to be concordant for RA than dizygotic twins.

The class II major histocompatibility complex allele HLA-DR4 and related alleles are known to be major genetic risk factors for RA. Early studies showed that as many as 70% of patients with RA express HLA-DR4 compared with 28% of control individuals (Panayi *et al*, 1978; Stastny, 1978). This association is particularly strong for individuals who develop RA associated with antibodies to cyclic citrullinated polypeptides (CCP). An association with HLA-DR4 has been noted in many populations, except Israeli Jews, Asian Indians, and Yakima Indians of North America. In these individuals, there is an association between RA and the closely related HLA-DR1 (Schiff *et al*, 1982).

ENVIRONMENTAL FACTORS

Increasing urbanization and industrialization in Europe from 18th century onwards led to the spread of rheumatic diseases. Such a demographic change in the prevalence of RA seems to have been observed in South Africa.

PATHOPHYSIOLOGY

Rheumatoid arthritis is a form of autoimmunity, the causes of which are still incompletely known.

The key evidences relating to pathogenesis are:

1. A genetic link with HLA-DR4 and related allotypes of MHC Class II and the T cell-associated protein PTPN22.

2. A link with cigarette smoking that appears to be causal.

3. A remarkable deceleration of disease progression in many cases by blockade of the cytokine TNF (alpha).

4. A similar dramatic response in many cases to depletion of B lymphocytes, but no comparable response to depletion of T lymphocytes.

5. A more or less random pattern of whether and when predisposed individuals are affected.

6. The presence of autoantibodies to IgGFc, known as rheumatoid factors (RF), and antibodies to cyclic citrullinated peptides (CCP).

If TNF release is stimulated by B cell products in the form of RF or ACPA -containing immune complexes, through activation of immunoglobulin Fc receptors, then RA can be seen as a form of Type III hypersensitivity.[20] If TNF release is stimulated by T cell products such

as interleukin-17 it might be considered closer to type IV hypersensitivity although this terminology may be getting somewhat dated and unhelpful.

It has long been suspected that certain infections could be triggers for this disease. The "mistaken identity" theory suggests that an infection triggers an immune response, leaving behind antibodies that should be specific to that organism. The antibodies are not sufficiently specific, though, and set off an immune attack against part of the host. Because the normal host molecule "looks like" a molecule on the offending organism that triggered the initial immune reaction—this phenomenon is called molecular mimicry. Epidemiological studies have confirmed a potential association between RA and two herpes virus infections: Epstein-Barr virus (EBV) and Human Herpes Virus 6 (HHV-6).[23] Individuals with RA are more likely to exhibit an abnormal immune response to the Epstein-Barr virus.[24,25]

PATHOLOGY

Disease in the joints

Microvascular injury and an increase in the number of synovial lining cells appear to be the earliest lesions in rheumatoid synovitis. Subsequently, perivascular infiltration with mononuclear cells is seen. Before the onset of clinical symptoms, the perivascular infiltrate is predominantly composed of myeloid cells, whereas in symptomatic

arthritis, T cells can also be found, although their number does not appear to correlate with symptoms. As the process continues, the synovium becomes edematous and protrudes into the joint cavity as villous projections.[2]

Light-microscopic examination discloses a characteristic constellation of features, which include hyperplasia and hypertrophy of the synovial lining cells; focal or segmental vascular changes, including microvascular injury, thrombosis, and neovascularization; edema; and infiltration with mononuclear cells, often collected into aggregates around small blood vessels. Rheumatoid synovial endothelial cells express increased amounts of various adhesion molecules involved in the process. The mononuclear cell collections are variable in composition and size. The predominant infiltrating cell is the T lymphocyte. CD4+ T cells predominate over CD8+ T cells and are frequently found in close proximity to HLA-DR+ macrophages and dendritic cells.

Both polyclonal immunoglobulin and the autoantibody rheumatoid factor are produced within the synovial tissue, which leads to the local formation of immune complexes. Antibodies to synovial tissue components may also contribute to inflammation. Recent evidence suggests that antibodies to CCP, which are generated within the synovium, may contribute to RA synovitis. Increased numbers of

activated mast cells are also found in the rheumatoid synovium. Local release of the contents of their granules may contribute to inflammation. Finally, the synovial fibroblasts in RA manifest evidence of activation in that they produce a number of enzymes such as collagenase and cathepsins that can degrade components of the articular matrix. These activated fibroblasts are particularly prominent in the lining layer and at the interface with bone and cartilage. Osteoclasts are also prominent at sites of bone erosion.

Extra articular diseases

The most frequent tissue lesion is the subcutaneous granulomata. It is histologically more characteristic (moore & wilikens, 1977). These are found in 20% cases, usually seropositive.

Subcutaneous nodules have a characteristic histological appearance. There is a central area of fibinoid material consisting of swollen and fragmented collagen fibers, fibinoid exudates and cellular debris, surrounded by a palisade or radically arranged proliferating mononuclear cells. The nodules have a loose capsule of fibrous tissue.[6]

Similar granulomatous lesion may also occur in the pleura, lung, pericardium and sclera. Lymph nodes are often hyperplastic, showing

many lymphoid follicles with large germinal centers and numerous plasma cells in the sinuses and medullary cords. Immunofluorescence shows that plasma cells in the synovium and lymph nodes synthesis rheumatoid factors.

The 1987 revised criteria (ACR) for the classification of rheumatoid arthritis (RA) [1].

1. **Morning stiffness**:

This occurs in and around the joints and lasts at least 1 hour before maximal improvement.

2. Arthritis of 3 or more joint areas:

At least 3 joint areas simultaneously have soft-tissue swelling or fluid (not bony overgrowth) observed by a physician. The 14 possible areas include the right and left proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle, and metatarsophalangeal (MTP) joints.

3. Arthritis of hand joints:

At least one area in a wrist, MCP, or PIP joint is swollen.

4. **Symmetric arthritis**:

Simultaneous involvement of the same joint areas on both sides of the body. Bilateral involvement of PIPs, MCPs, and MTPs is acceptable without absolute symmetry.

5. **Rheumatoid nodules**:

Subcutaneous nodules are present over bony prominences or extensor surfaces or in juxta-articular regions.

6. Serum Rheumatoid Factor:

Abnormal amounts of serum RF are demonstrated by any method for which the result has been positive in fewer than 5% of healthy control subjects.

7. Radiographic changes:

Typical changes of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints: Osteoarthritic changes alone do not qualify.

The presence of 4 criteria supports the diagnosis of RA[1]. Criteria 1-4 must be present for at least 6 weeks, and a physician must observe criteria 2-5. These criteria are intended as a guideline for classification of patients, often for research purposes. They do not absolutely confirm or exclude a diagnosis of RA in a particular patient, especially in those with early arthritis.

Articular manifestations of Rheumatoid Arthritis:

Pain, swelling, and tenderness may initially be poorly localized to the joints. Pain in affected joints, aggravated by movement, is the most

common manifestation of established RA. Generalized stiffness is frequent and is usually greatest after periods of inactivity. Pain originates predominantly from the joint capsule, which is abundantly supplied with pain fibers and is markedly sensitive to stretching or distension. Joint swelling results from accumulation of synovial fluid, hypertrophy of the synovium, and thickening of the joint capsule.

Although inflammation can affect any diarthrodial joint, RA most often causes symmetric arthritis with characteristic involvement of certain specific joints such as the proximal interphalangeal and metacarpophalangeal joints. The distal interphalangeal joints are rarely involved. Synovitis of the wrist joints is a nearly uniform feature of RA and may lead to limitation of motion, deformity, and median nerve entrapment (carpal tunnel syndrome). Synovitis of the elbow joint often leads to flexion contractures that may develop early in the disease. The knee joint is commonly involved with synovial hypertrophy, chronic effusion, and frequently ligamentous laxity. Arthritis in the forefoot, ankles, and subtalar joints can produce severe pain with ambulation as well as a number of deformities.

Axial involvement is usually limited to the upper cervical spine. Involvement of the lumbar spine is not seen, and lower back pain cannot be ascribed to rheumatoid inflammation. On occasion, inflammation from

the synovial joints and bursae of the upper cervical spine leads to atlantoaxial subluxation. This usually presents as pain in the occiput but on rare occasions may lead to compression of the spinal cord.

With persistent inflammation, a variety of characteristic joint changes develop. These can be attributed to a number of pathologic events, including laxity of supporting soft tissue structures; damage or weakening of ligaments, tendons, and the joint capsule; cartilage degradation; muscle imbalance; and unopposed physical forces associated with the use of affected joints.

Characteristic changes of the hand include (1) radial deviation at the wrist with ulnar deviation of the digits, often with palmar subluxation of the proximal phalanges ("Z" deformity); (2) hyperextension of the proximal interphalangeal joints, with compensatory flexion of the distal interphalangeal joints (swan-neck deformity); (3) flexion contracture of the proximal interphalangeal joints and extension of the distal interphalangeal joints (boutonnière deformity); and (4) hyperextension of the first interphalangeal joint and flexion of the first metacarpophalangeal joint with a consequent loss of thumb mobility and pinch.

Typical joint changes may also develop in the feet, including eversion at the hindfoot (subtalar joint), plantar subluxation of the metatarsal heads, widening of the forefoot, hallux valgus, and lateral

deviation and dorsal subluxation of the toes. Later in the disease, disability is more related to structural damage to articular structures.

Extraarticular Manifestations:

It is estimated that as many as 40% of patients may have extraarticular manifestations, and in 15% these are severe. On occasion, extraarticular manifestations may be the major evidence of disease activity and source of morbidity and require management per se. As a rule, these manifestations occur in individuals with high titers of autoantibodies to the Fc component of immunoglobulin G (rheumatoid factors) or with antibodies to CCP.

Rheumatoid nodules may develop in 20–30% of persons with RA. They are usually found on periarticular structures, extensor surfaces, or other areas subjected to mechanical pressure, but they can develop elsewhere, including the pleura and meninges. Common locations include the olecranon bursa, the proximal ulna, the Achilles tendon, and the occiput. They are found almost invariably in individuals with circulating rheumatoid factor. Histologically, rheumatoid nodules consist of a central zone of necrotic material including collagen fibrils, noncollagenous filaments, and cellular debris; a midzone of palisading macrophages that express HLA-DR antigens; and an outer zone of granulation tissue[2].

Rheumatoid vasculitis, which can affect nearly any organ system, is seen in patients with severe RA and high titers of circulating rheumatoid factor. In its most aggressive form, rheumatoid vasculitis can cause polyneuropathy and mononeuritis multiplex, cutaneous ulceration and dermal necrosis, digital gangrene, and visceral infarction.

Rheumatoid arthritis patients are more prone to atherosclerosis, and risk of myocardial infarction[7] and stroke is markedly increased.[8] Other complications that may arise include: pericarditis, endocarditis, left ventricular failure, valvulitis and fibrosis

Renal amyloidosis can occur as a consequence of chronic inflammation. Rheumatoid arthritis may affect the kidney glomerulus directly through a vasculopathy or a mesangial infiltrate but this is less well documented. Treatment with Penicillamine and gold salts are recognized causes of membranous nephropathy.

The eye is directly affected in the form of episcleritis which when severe can very rarely progress to perforating scleromalacia. Rather more common is the indirect effect of keratoconjunctivitis sicca, which is dryness of eyes and mouth caused by lymphocyte infiltration of lacrimal and salivary glands. When severe, dryness of the cornea can lead to keratitis and loss of vision. Preventive treatment of severe dryness with measures such as nasolacrimal duct occlusion is important.

Felty's syndrome consists of chronic RA, splenomegaly, neutropenia, and, on occasion, anemia and thrombocytopenia. It is most common in individuals with long-standing disease. It may develop after joint inflammation has regressed. Circulating immune complexes are often present, and evidence of complement consumption may be seen. The leucopenia is a selective neutropenia with polymorphonuclear leukocyte counts of < 1500 cells /L. Bone marrow examination usually reveals moderate hypercellularity with a paucity of mature neutrophils[2].

RA tends to spare the central nervous system directly, although vasculitis can cause peripheral neuropathy. *Neurologic manifestations* may also result from atlantoaxial or midcervical spine subluxations. Nerve entrapment secondary to proliferative synovitis or joint deformities may produce neuropathies of median, ulnar, radial (interosseous branch), or anterior tibial nerves.

Anemia is by far the most common abnormality of the blood cells. Rheumatoid arthritis may cause a warm autoimmune hemolytic anemia[10]. The red cells are of normal size and colour (normocytic and normochromic). The mechanism of neutropenia is complex. An increased platelet count (thrombocytosis) occurs when inflammation is uncontrolled, as does the anemia.

Local osteoporosis occurs in RA around inflamed joints. It is postulated to be partially caused by inflammatory cytokines. More general osteoporosis is probably contributed to by immobility, systemic cytokine effects, local cytokine release in bone marrow and corticosteroid therapy.

Laboratory investigations:

Rheumatoid Factor:

It is an auto antibody (usually of IgM class) against the Fc portion of IgG and found in about 85% of patients with disease[11]. The presence of rheumatoid factor does not establish the diagnosis of RA as the predictive value of the presence of rheumatoid factor in determining a diagnosis of RA is poor. Therefore, the rheumatoid factor test is not useful as a screening procedure. However, the presence of rheumatoid factor can be of prognostic significance because patients with high titers tend to have more severe and progressive disease with extraarticular manifestations. Rheumatoid factor is uniformly found in patients with nodules or vasculitis.

Antibodies to CCP (Anti-CCP) can also be used to evaluate patients with RA. Although these antibodies are most commonly found in rheumatoid factor–positive patients, on occasion they can be detected in the absence of rheumatoid factor. In addition, the anti-CCP test has a

similar sensitivity and a better specificity for RA than does rheumatoid factor, and, therefore, some have advocated its use to evaluate RA patients instead of rheumatoid factor[12]. This is particularly the case in individuals with early RA, in whom assessment of anti-CCP may be the most useful to confirm the diagnosis and establish a likely prognosis. The presence of anti-CCP is most common in persons with aggressive disease, with a tendency for developing bone erosions.

Recently a serological point-of-care test (POCT)[13] for the early detection of RA has been developed. This assay combines the detection of rheumatoid factor and anti-MCV (Anti Mutated Citrulinated Vimentin) for diagnosis of rheumatoid arthritis and shows a sensitivity of 72% and specificity of 99.7%[14].

The erythrocyte sedimentation rate (ESR) is increased in nearly all patients with active RA. The levels of a variety of other acute-phase reactants including ceruloplasmin and C-reactive protein are also elevated, and generally such elevations correlate with disease activity.

Synovial fluid analysis confirms the presence of inflammatory arthritis, although none of the findings is specific. The fluid is usually turbid, with reduced viscosity, increased protein content, and a slightly decreased or normal glucose concentration.

A synovial fluid white blood cell count >2000/ L with >75% polymorphonuclear leukocytes is highly characteristic of inflammatory arthritis, although not diagnostic of RA.

Radiological findings:

In Rheumatoid arthritis, there may be no changes in the early stages of the disease, or the x-ray may demonstrate juxta-articular osteopenia, soft tissue swelling and loss of joint space. As the disease advances, there may be bony erosions and subluxation.

Magnetic resonance imaging and ultrasound are also used in rheumatoid arthritis. There have been technical advances in ultrasonography. High-frequency transducers (10 MHz or higher) have improved the spatial resolution of Ultrasound images; these images can depict 20% more erosions than conventional radiography. Also, color Doppler and power Doppler ultrasound, which show vascular signals of active synovitis, are useful in assessing synovial inflammation. This is important, since in the early stages of rheumatoid arthritis, the synovium is primarily affected, and synovitis seems to be the best predictive marker of future joint damage.[15]

Management of Rheumatoid Arthritis:

The goals of therapy of RA include relief of pain, reduction of inflammation, protection of articular structures, maintenance of function, and control of systemic involvement[2]. Management of patients with RA involves an interdisciplinary approach, which attempts to deal with the various problems that these individuals encounter with functional as well as psychosocial interactions.

DRUG THERAPY[18]: Five groups of drugs are commonly used.

i. Use of **Nonsteroidal anti-inflammatory drugs (NSAIDs)** and simple analgesics to control the symptoms and signs of the local inflammatory process. These agents are rapidly effective at mitigating signs and symptoms, but they appear to exert minimal effect on the progression of the disease.

ii. **Low-dose oral Glucocorticoids**: An initial course of low-dose glucocorticoids should be considered in patients either alone or with disease modifying anti-rheumatic drugs (DMARDs)[19]. Intraarticular glucocorticoids can often provide transient symptomatic relief when systemic medical therapy has failed to resolve inflammation.

iii. **DMARDs:** These agents appear to have the capacity to decrease elevated levels of acute-phase reactants in treated patients and, therefore, are thought to modify the inflammatory component of RA and thus its

destructive capacity. These agents include methotrexate, sulfasalazine, hydroxychloroquine, gold salts, or D-penicillamine.

iv. **Biologics**[16]: which include TNG-neutralizing agents (infliximab, etanercept, and adalimumab), IL-1-neutralizing agents (anakinra), those that deplete B cells (rituximab)[17], and those that interfere with T cell activation (abatacept). These agents have been shown to have a major impact on the signs and symptoms of RA and also to slow progressive damage to articular structures.

v. **Immunosuppressive and cytotoxic drugs**: include leflunomide, cyclosporine, azathioprine, and cyclophosphamide.

Substituting omega-3 fatty acids such as eicosapentaenoic acid found in certain fish oils for dietary omega-6 essential fatty acids found in meat has also been shown to provide symptomatic improvement in patients with RA[2.]

PULMONARY MANIFESTATIONS IN RHEUMATOID ARTHRITIS:

Pulmonary manifestations of RA were first described in 1948, when Ellman and Ball recognized diffuse pulmonary fibrosis in three patients with RA.[31] Pulmonary disease, which is a major source of morbidity and mortality in RA, manifests most commonly as interstitial lung disease (ILD), airways disease, rheumatoid nodules, and pleural

effusions. Respiratory manifestations usually become more prevalent as RA progresses, but they may present simultaneously with joint symptoms or even predate joint involvement.[28] Many pulmonary manifestations are directly linked to RA itself and may be a result of underlying defects in immunity and chronic inflammation.[29]Some are due to exposures and to the treatment of RA with disease-modifying antirheumatic drugs (DMARDs).[30] In unselected populations, up to a third of subjects describe important respiratory symptoms[35], but two-thirds or more may have significant radiographic abnormalities on high-resolution computed tomography (HRCT).

PARENCHYMAL LUNG DISEASE

PULMONARY NODULES:

Rheumatoid nodules (necrobiotic nodules) are found in up to 20% of patients .[21] Nodules typically range from a millimeter to centimeters in size, and are usually asymptomatic. However, complications include pneumothorax, hydropneumothorax, sterile empyema, and hemoptysis. Nodules identified on HRCT must be distinguished from malignant and infectious lesions.

Caplan's syndrome refers to conglomerations of nodules seen in patients with the combination of RA and pneumoconiosis.[22]

INTERSTITIAL LUNG DISEASE

The prevalence of interstitial lung disease (ILD) varies depending on the criteria used to establish the diagnosis. In retrospective studies, clinically significant ILD has been described in approximately 7% of subjects [33], whereas autopsy studies have described a prevalence of up to 35% [34]. Prospective studies that use HRCT, the most sensitive technique for the detection of RA-related lung disease[35], to specifically screen for disease have shown a much higher prevalence. In unselected populations, specific features of ILD will be seen in up to two-thirds of individuals [36].

Unlike most other connective tissue diseases, the usual interstitial pneumonia (UIP) pattern is more commonly seen on surgical lung biopsy than nonspecific interstitial pneumonia (NSIP). Lymphocytic interstitial pneumonia (LIP) and organizing pneumonia (OP) have also been described[37]. Acute interstitial pneumonia (Haman-Rich syndrome), on the other hand, is quite uncommon, but presents with a rapid and aggressive course that frequently results in death.

PREDICTORS OF THE DEVELOPMENT OF RA-ILD

Clinical, genetic, and environmental factors have been used to predict the development of lung disease in RA. Risk factors for the development of RA-ILD include older age, male sex, and a history of cigarette smoking. Sex influences both the risk as well as the pattern of

organ involvement. Both rheumatoid nodules and RA-ILD are more commonly seen in men.[38] Active or previous tobacco smoking is an independent risk factor for the development of RA[39], its severity, and its rheumatoid factor (RF) seropositivity[40]. A mechanistic connection has also been proposed for a relationship between tobacco smoke, the HLA-DRB1 "shared epitope" (SE), anticyclic citrullinated peptide antibody (anti-CCP), and the development of RA[41]. The combination of a history of tobacco smoking and the presence of two copies of the HLA-DR SE genes increased the risk for RA 21-fold compared with the risk among nonsmokers carrying no SE genes. Smoking has been independently associated with the development of radiographic and physiologic abnormalities consistent with ILD.

Patients with anti-CCP antibodies or IgA and/or IgM RF autoantibodies represent a group at highest risk for the development of clinically significant articular and extraarticular RA [42]. High-titer RF has been associated with the presence of RA-ILD and a decreased DL_{CO}.[43] The role of anti-CCP antibodies in the lung is unknown.

Pathology

A cellular inflammatory process is required for and initiates a secondary fibroproliferative process, which may become progressive and independent of its initiating cause. In patients with hypersensitivity

pneumonitis , reversible granulomatous inflammation is generally seen. However, once the fibroproliferative process begins, the clinical course and gene expression profile become similar to those of IPF, the prototypical fibrosing lung disease, and the disease becomes unresponsive to immunosuppression.[44,45]

Histologically in early stages an interstitial infiltrate predominates, composed of lymphocytes, plasma cells and histiocytes.[9] With progression the infiltrate is replaced by fibrous tissue. Immunofluroscence studies demonstrate Ig, largely IgM in alveolar and arterial walls. Immune complex deposition in the lung interstitium and alveolar walls contributes to alveolar macrophage activation. It may play a role in enhancing the pathogenicity of immune complex mediated injury in the lungs as ILD in rheumatoid arthritis is commonly seen in patients with high titers of rheumatoid factor.

The presence of areas of lymphoplasmacytic infiltrate is associated with physiologic improvement in response to cyclophosphamide and corticosteroid therapy, whereas fibroblast foci and areas of airspace organization were associated with a decline in function[46.]

CURRENT THERAPIES FOR RA-ILD

The effective treatment of the joint disease should not be used as a surrogate for beneficial or even adequate treatment of the ILD. Tumor necrosis factor-alpha antagonist therapy has been hinted to slow the progression of RA-related pulmonary fibrosis[47], it has also been associated with the development of fulminate respiratory failure[48]. In several case reports, corticosteroids have been suggested as a treatment of the ILD characterized by organizing pneumonia pathologic pattern [49]. Cyclosporine has been used to treat both acute pneumonitis and progressive pulmonary fibrosis with success in individual patients .[50] The use of rituximab and abatacept for the treatment of refractory RA synovitis is supported by current data, but their use in the treatment of the pulmonary manifestations of RA remains unclear [51.]

Mycophenolate moefetil has recently been reported in small case series to have a beneficial effect on CTD-ILD, and may be considered in this setting.[53] Rapidly progressive or extensive disease with arterial hypoxemia is often treated with either daily oral or monthly intravenous cyclophosphamide in combination with corticosteroids.[52] Patients with severe, fibrotic lung disease should be considered for referral for lung transplantation. Given the clinical impact of RA-ILD, and the absence of

definitive data on its treatment, prospective, controlled studies are necessary to guide the field.

PLEURAL DISEASES

Pleurisy, pleuritis, and effusions occur in approximately 5% of patients [54] The most common pulmonary manifestation of RA is pleural effusion. Effusions tend to be small, asymmetric, and to wax and wane. Pleural fluid analysis generally reveals a low glucose (< 50 mg/dl), low pH (< 7.30), high lactate dehydrogenase (LDH) (> 1,000), and high rheumatoid factor titers.[55] Effusions in patients with RA cannot be assumed to be RA associated; infections, empyema, sterile empyema, chylothorax, and congestive heart failure (CHF) are all seen.

Asymptomatic pleural effusions need not be treated. For patients with RA who have symptomatic pleural effusions, various studies have reported that repeated thoracentesis, pleurodesis (using either talc, bleomycin, or tetracycline), and administration of corticosteroids can be beneficial[56].

AIRWAY DISEASES: (CRICOARYTENOID ARTHRITIS, BRONCHIECTASIS, BRONCHIOLITIS)

RA can cause upper, lower, and small, distal airway disease.[57] Cricoarytenoid arthritis may present with hoarseness, pain, change in voice, or globus. Upper airway complications, such as rheumatoid nodules and vocal cord paresis, also occur. There is a high incidence of radiographic bronchiectasis, up to 30% in some HRCT studies[58]; however, clinically significant disease is much less frequent. Symptoms are identical to other causes of bronchiectasis and include cough, sputum production, frequent episodes of infection, and hemoptysis. Small airway disease with physiologic obstruction is common[59], and presents with exertional dyspnea, a nonproductive cough, or wheezing. HRCT is suggestive of small airway disease when it demonstrates centrilobular nodules, hyperinflation, and heterogenous air trapping. Pathologically, both fibrosing (obliterative or constrictive bronchiolitis) and cellular (diffuse pan bronchiolitis and follicular bronchiolitis) have been well described.[60]

BRONCHIECTASIS:

The prevalence of bronchiectasis in RA ranges from 30% to 58% when detected by HRCT.[68] HRCT is more sensitive than respiratory symptoms, PFTs, or chest radiograph for the presence of bronchiectasis.

Both cylindrical and traction bronchiectasis occur and may accompany RA-ILD. Clinically evident bronchiectasis is much less frequent (1%–5% of RA patients) and may precede the onset of the articular symptoms and the diagnosis of RA.[69] The high prevalence of bronchiectasis in RA may be the result of defects in humoral immunity, with increased susceptibility to respiratory infections, and subsequent structural damage to the airways.[70]Genetic predisposition may also play a role. Overall survival may be decreased in RA patients with bronchiectasis, predominantly due to infections and acute respiratory failure. Bronchiectasis tends to develop late in RA, particularly in women with RF seropositive and nodular disease.

BRONCHIOLITIS OBLITERANS (BO):

Bronchiolitis obliterans (BO) is disorder of the small airways, pathologically characterized by obliterative bronchiolitis with circumferential narrowing, ulceration, and scarring of the terminal and respiratory bronchioles. BO is characterized clinically by progressive dyspnea accompanied by dry cough.[61] hyperinflation and air trapping may be present, although in later stages of disease, both restrictive and obstructive physiology due to the severity of the air trapping may be observed. HRCT may be more sensitive than PFTs for detecting small airways disease. The radiographic appearance is that of moderate to

severe air trapping, as demonstrated by a mosaic pattern of patchy or segmental regions of decreased lung attenuation that are accentuated on expiratory images BO generally has a poor prognosis, with inexorable progression and poor response to corticosteroids[61].

PULMONARY VASCULAR DISEASE:

Rheumatoid pulmonary vascular involvement produces pulmonary vasculitis, primary and secondary pulmonary hypertension. Secondary pulmonary hypertension may result due to advanced interstitial lung disease.

Diffuse alveolar hemorrhage (DAH) due to pulmonary capillaritis has been described in association with RA but is extremely rare.[62] HRCT features include diffuse ground-glass opacities and alveolar opacities, which are relatively nonspecific findings and can appear similar to pulmonary edema, diffuse infection, or a drug reaction. The diagnosis of DAH is confirmed in the correct clinical setting by bronchoscopy with BAL, in which progressively bloodier fluid is obtained on serial lavage specimens.

DRUG INDUCED LUNG INJURY:

The mechanism of methotrexate-related pulmonary toxicity is unknown. However, it is thought to be an idiosyncratic or hypersensitivity reaction rather than being related to cumulative dose[63].

Although it is not possible to predict which patients will develop pulmonary toxicity, patients with underlying rheumatoid pleural or pulmonary disease may be at increased risk. Clinical presentations vary and may include the indolent onset of pulmonary fibrosis, acute lung injury with diffuse alveolar damage (DAD), rapidly progressive pulmonary fibrosis, pleuritis, pleural effusions, nodulosis, or bronchitis with airways hyperreactivity and cough[64,65] Distinguishing methotrexate toxicity from infection and RA-ILD is difficult. On surgical lung biopsy, several different pathologic patterns may be consistent with drug toxicity, including cellular interstitial infiltrates, granulomas, infiltration with eosinophils, and a diffuse alveolar damage pattern with concomitant perivascular inflammation[66.] Therapy is mainly supportive, usually starting with withdrawal of methotrexate therapy alone, although often empirical antibiotic therapy is also administered. In severe cases, corticosteroids may be used; for some patients, other immunosuppressive therapy, such as azathioprine or cyclophosphamide, may be required.

Gold-induced pneumonitis manifests typically with rapid onset of cough, fever, and dyspnea, usually within the first 6 months of therapy. D-Penicillamine has been associated with ILD, BO, and a pulmonary-renal syndrome with alveolar Hemorrhage[67.] Toxicity has been associated with peripheral blood eosinophilia and elevated serum IgE levels.

PULMONARY FUNCTION TESTS:

Pulmonary function testing is a valuable tool for evaluating the respiratory system, representing an important adjunct to the patient history, various lung imaging studies, and invasive testing such as bronchoscopy and open-lung biopsy. Insight into underlying pathophysiology can often be gained by comparing the measured values for pulmonary function tests obtained on a patient at any particular point with normative values derived from population studies. The percentage of predicted normal is used to grade the severity of the abnormality. Pulmonary function tests (PFTs) is a generic term used to indicate a battery of studies or maneuvers that may be performed using standardized equipment to measure lung function. PFTs can include simple screening spirometry, formal lung volume measurement, diffusing capacity for carbon monoxide, and arterial blood gases. Pulmonary function studies measure and record the properties of four lung components. These include the airways (large and small), lung parenchyma (alveoli, interstitium), pulmonary vasculature, and the bellows-pump mechanisms.

Spirometry:

Spirometry is the most commonly used lung function screening study. A spirogram is a graphic representation of bulk air movement depicted as a volume-time tracing or as a flow-volume tracing. Values

generated from a simple spirogram provide important graphic and numeric data regarding the mechanical properties of the lungs, including airflow (forced expiratory volume in 1 second [FEV_1]) and exhaled lung volume (FVC). The most common parameters measured in Spirometry are Vital capacity (VC), Forced vital capacity (FVC), Forced expiratory volume (FEV) at timed intervals of 0.5, 1.0 (FEV1), 2.0, and 3.0 seconds, Forced expiratory flow 25–75% (FEF 25–75) and Maximal voluntary ventilation (MVV).

Results are usually given in both raw data (litres, litres per second) and percent predicted - the test result as a percent of the "predicted values" for the patients of similar characteristics (height, age, sex, race and weight). The interpretation of the results can vary depending on the physician and the source of the predicted values. Generally speaking, results nearest to 100% predicted are the most normal and results over 80% are often considered normal[71].

Data from a spirogram provide important clues to help distinguish obstructive pulmonary disorders that typically reduce airflow, such as asthma and emphysema, from restrictive disorders that typically reduce total lung volumes, including pulmonary fibrosis and neuromuscular disease.

Forced Expiratory Volume in one Second (FEV1):

The FEV_1 is the most widely used parameter to measure the mechanical properties of the lungs. In normal persons, the FEV_1 accounts for the greatest part of the exhaled volume from a spirometric maneuver and reflect mechanical properties of the large and the medium-sized airways. In a normal flow-volume loop, the FEV_1 occurs at about 75% to 85% of the FVC. This parameter is reduced in obstructive and restrictive disorders.

Forced Vital Capacity

FVC is a measure of lung volume and is usually reduced in diseases that cause the lungs to be smaller. Such processes are generally termed restrictive and can include disorders of the lung parenchyma, such as pulmonary fibrosis, or of the bellows, including kyphoscoliosis, neuromuscular disease, and pleural effusion. However, a reduction in FVC is not always due to reduced total volumes and can occur in the setting of large lungs hyperinflated due to severe airflow obstruction and air trapping, as in emphysema. This phenomenon referred to as *pseudo restriction*. Reduced FVC can occur despite a normal or increased total lung volume. Therefore, FVC is not a reliable indicator of total lung capacity or restriction, especially in the setting of airflow obstruction. The overall accuracy of the FVC for restriction is about 60%.[74]

FEV1/FVC ratio (FEV1%)

In healthy adults this should be approximately 75–80%. In obstructive diseases (asthma, COPD, chronic bronchitis, emphysema) FEV_1 is diminished because of increased airway resistance to expiratory flow and the FVC may be decreased (for instance by premature closure of airway in expiration). This generates a reduced value (<80%, often ~45%). In restrictive diseases (such as pulmonary fibrosis) the FEV_1 and FVC are both reduced proportionally and the value may be normal or even increased as a result of decreased lung compliance.

Forced Expiratory Flow (FEF)

Forced Expiratory Flow (FEF) is the flow (or speed) of air coming out of the lung during the middle portion of a forced expiration. It can be given at discrete times, generally defined by what fraction remains of the functional vital capacity (FVC). The usual intervals are 25%, 50% and 75% (FEF25, FEF50 and FEF75), or 25% and 50% of FVC. It can also be given as a mean of the flow during an interval, also generally delimited by when specific fractions remain of FVC, usually 25–75% (FEF25–75%).[72] FEF 25–75% or 25–50% gives an indication of what is happening in the lower airways. It is a more sensitive parameter and not as reproducible as the others. It is a useful serial measurement because it

will be affected before FEV1, so can act as an early warning sign of small airway disease.

MMEF or **MEF** stands for maximal (mid) expiratory flow and is the peak of expiratory flow as taken from the flow-volume curve and measured in liters per second. It should theoretically be identical to peak expiratory flow (PEF), which is, however, generally measured by a peak flow meter and given in liters per minute.[73]

MEASUREMENT	OBSTRUCTIVE PATTERN	RESTRICTIVE PATTERN
FVC	Reduced or normal	reduced
FEV1	reduced	normal or reduced
FEV1/FVC	reduced	normal or increased
TLC	normal or increased	reduced

Diffusing Capacity

Spirometry and lung volumes elucidate the mechanics of ventilation but do not address the gas-transfer function of the lung. With use of a highly diffusable gas (carbon monoxide [CO]) as a surrogate for oxygen, the diffusing capacity of lung for CO (DLCO) estimates the patient's ability to absorb alveolar gases. Diffusion in the lungs is most efficient when the surface area for gas transfer is high and the blood is readily able to accept the gas being transferred. It is thus decreased in:

• Conditions that minimize the ability of the blood to accept and bind the gas that is diffusing (eg, anemia)

• Conditions that decrease the surface area of the alveolar-capillary membrane (eg, emphysema, pulmonary embolism)

• To a smaller degree, conditions that alter the membrane's permeability or increase its thickness (eg, pulmonary fibrosis).

Conversely, conditions resulting in an increased effective pulmonary blood volume cause an elevated DLCO[75].

The gas used to test the diffusing capacity must be more soluble in blood than in lung tissue. Ideally, the amount of gas entering the blood should be limited by the lungs' ability to transfer it and not by lung perfusion (i.e., the gas must avidly bind to hemoglobin). Carbon monoxide is the gas used, as it most closely meets these requirements.[76]

In RA-ILD, PFTs typically show restrictive physiology and diffusion impairment. A defect in DLCO is often the earliest PFT finding in RA-ILD.[77] Exercise testing is rarely used for screening; however, it is important to ambulate patients with RA-ILD because resting oximetry may be falsely reassuring. Oxygen desaturation on 6-minute walk testing is predicted by abnormalities in lung function.[78]

There are 2 major mechanisms for exertional hypoxemia in ILD. First, an inappropriate decrease in DLCO during exercise due to

inadequate pulmonary capillary recruitment leads to a relatively smaller capillary blood volume and subsequently reduced time available for gas exchange.[79] Second, patients with ILD have a reduced mixed venous oxygen content due to areas of ventilation/ perfusion mismatch and intrapulmonary shunt.[79] Late in disease, fibrosis and pulmonary vascular obliteration lead to severe diffusion abnormalities, with resting arterial hypoxemia and profound exertional desaturation.

Chest Radiography:

Evidence of interstitial fibrosis is seen at chest radiography in approximately 5% of patients with rheumatoid arthritis . The chest radiograph may be normal in patients with early fibrosis. In late stages, chest radiograph shows changes identical to that of Interstitial Pulmonary Fibrosis (IPF). Chest radiographs typically show a fine reticular or reticulonodular pattern involving the lower lung zones in early stages. With progression of disease, the reticular pattern becomes more coarse and diffuse, and honeycombing may be seen .It is useful in detecting clinically significant pleural effusion and rheumatoid nodules.

High resolution computed tomography:

The use of cross sectional images in CT makes it possible to distinguish between densities and provide accurate size assessment of lesions. With high resolution CT, the thickness of individual cross

sectional images is approximately 1 to 2 mm rather than the usual 10 mm and the images are reconstructed with high spatial resolution algorithms.

HRCT is the gold standard for diagnosis of ILD[80]. On HRCT, the appearance of RA with interstitial fibrosis is usually indistinguishable from that of IPF and includes traction bronchiectasis, intralobular septal thickening, irregular interlobular septal thickening, irregular interfaces, honeycombing, Ground Glass Opacities (GGO), peripheral and subpleural predominance of fibrosis or GGO, lower lung zone and posterior predominance, pleural thickening and effusion. Honeycombing is seen less commonly than in IPF; however predominant GGO is seen more commonly in patients with RA. Evidence of GGO as a predominant finding in the absence of honeycombing is associated with active alveolitis. This is usually considered a feature of early and potentially reversible disease. Radiographically abnormalities are indistinguishable from ILD caused by other diseases. Progression to end-stage fibrosis results in the classical honeycombing pattern. Coexisting pleural effusion is common. HRCT is much more sensitive than plain chest radiography in the assessment of ILD and its higher sensitivity should allow an earlier diagnosis[81]. The coexistence of airway thickening and dilatation outside the fibrotic area is also highly suggestive of RA. HRCT shows similar lesions, including GGO, basal honeycombing, traction bronchiectasis and

emphysema.[82] Other changes of RA on HRCT include BOOP, bronchiectasis and bronchial disease, consolidation, enlarged lymph nodes and nodules that are predominantly subpleural in location. Bronchiectasis is seen in up to a third of patients.

In RA, it is common to see several histopathologic and/or radiographic patterns simultaneously, for example, the presence of airways disease or rheumatoid nodules in conjunction with ILD. When observed serially, HRCT manifestations in RA-ILD may include either acute exacerbations of disease, characterized by the onset of diffuse ground-glass opacities, or progressive fibrosis, characterized by increasing reticularity and honeycombing.[83]

BRONCHO ALVEOLAR LAVAGE:

The Bronchoscope can be used to sample material from the distal pulmonary parenchyma. The upper airway is anaesthetized and the bronchoscope is introduced and wedged into a subsegmental airway. Aliquots of sterile saline are introduced through the scope. This allows sampling of the cells and organisms from the alveolar spaces. The lavage is filtered and the cells are stained with Papanicolaou's method and differential count is performed.

The role of bronchoalveolar lavage (BAL) in connective tissue disease-associated ILD (CTD-ILD) is discussed in detail in the article by

Kowal-Bielecka and colleagues elsewhere in this issue. In RA-ILD, BAL has not proven useful for diagnosis.[84] Nonetheless, BAL is important in the evaluation of radiographic abnormalities, primarily in the evaluation of alternative diagnoses to RA-ILD, including drug reaction, diffuse alveolar hemorrhage, and opportunistic infection.[85] Bronchoscopy with BAL should be considered in the evaluation of new infiltrates in any RA patient receiving immunosuppressive therapy.

LUNG BIOPSY:

Surgical lung biopsy is not commonly obtained in RA patients. However, specific pathologic patterns may help determine prognosis and response to treatment. The pathologic patterns observed in RA-ILD are similar to those in the idiopathic interstitial pneumonias. However, certain findings, such as lymphoid hyperplasia and plasma cell infiltration, are more common in RA-ILD.[86] One notable feature of RA-ILD is that more than one pathologic process, and often several, may occur in the same biopsy specimen, making comparison among series particularly difficult.[87]

UIP and NSIP are the most common histopathologic patterns in RA .UIP is more common than NSIP. UIP is characterized by a heterogeneous pattern in which areas of normal lung are interspersed with areas of active fibrosis (known as fibroblastic foci), interstitial

inflammation, and honeycombing. The changes are usually most pronounced in the subpleural lung.

The features of NSIP, by contrast, are diffuse and spatially homogeneous[88]. There are 2 forms of NSIP: 1) cellular NSIP, which is characterized by lymphocytic and plasma cell infiltrates with minimal fibrosis; and 2) fibrotic NSIP, which is characterized by fibrotic changes, either alone or in combination with patchy areas of inflammation.

Organising Pneumonia is the primary pattern on biopsy in 10% to 22% of cases and is a secondary component in a significant number of RA-ILD cases.[86] This pattern may be primarily due to RA but can be caused by drug hypersensitivity, having been reported in association with methotrexate, etanercept, rituximab, and sulfasalazine.[65]

AIMS AND OBJECTIVES

1. To study the pulmonary manifestations of Rheumatoid arthritis.
2. To correlate the HRCT findings with pulmonary function test.

MATERIALS AND METHODS

Setting : Department of Medicine. Govt. Rajaji Hospital

Design : Cross Sectional Study.

Period of study : One year.

Ethical approval : Obtained from ethical committee, headed By Dean, Govt. Rajaji Hospital.

Consent : Obtained from all patients.

Statistical software : EPI Info 2008.

Study population : Patients attending Rheumatology OP with Rheumatoid Arthritis.

Inclusion criteria:

1) Patients who satisfied Revised American Rheumatologic Association criteria 1987, who have either respiratory symptoms or signs, irrespective of age, sex and duration of disease.

Exclusion criteria:

1) Previous history of Bronchial asthma/ Chronic Obstructive Airway Disease.
2) Patients with respiratory infections, including pulmonary tuberculosis.
3) Previous history of pulmonary tuberculosis.

4) Patients who are smokers.
5) Patients with occupation prone to develop occupational lung disease.
6) Those who have mixed disorder like SLE and RA; SS and RA; and MCTD and overlap syndrome.

Forty five patients attending Rheumatology clinic, Govt. Rajaji Hospital, Madurai, who were diagnosed to have Rheumatoid Arthritis, and having respiratory symptoms or signs were selected for the study.

The selected patients were evaluated with detailed history regarding the duration of disease, history of drug intake, type of onset of symptoms were noted.

Presence of joint swelling, tenderness and number of tender joints, number of swollen joints were noted. Detailed clinical examination was done especially for rheumatoid nodule and joint deformities. All systems were examined carefully and visual analogue pain score was carefully assessed. A detailed respiratory system examination was done with special attention to presence of pleural effusion, crepitations and wheeze.

Hemoglobin, White blood cell count, Differential count, Blood Urea, Serum Creatinine, Blood sugar, ESR, LFT, Rheumatoid Factor and C Reactive Protein by latex agglutination test and Chest X ray were done for all patients.

Disease Activity Score was calculated for every patients.

DAS 28 score

Disease activity score is a composite score using tender and swollen joint count, ESR and patient's global assessment activity using a 10 mm visual analogue scale.

DAS28= 0.56 √(tender joints) + 0.28√(swollen joints)
+ 0.70 Log (ESR) + 0.014(VAS in mm)

Classification

Mild ≤ 3.1

Moderate 3.2- 5.1

Severe > 5.1

(Minimum score= 0; Maximum score= 9)

After assessing baseline clinical and laboratory parameters, all patients were subjected to spirometric evaluation and High Resolution Computerized Tomography (HRCT).

The Spirometry was performed using Knudsen's computerized Spirometer. All the Spirometric parameters were expressed as percentage of predicted value for that particular age, sex, height, and weight comparable to South Indian population defined by Knudsen et al.

The entire test was repeated on three occasions and the best of the three readings were taken. Among the various spirometric parameters, the following were analyzed.

1. Forced Vital Capacity (FVC).
2. Forced Expiratory Volume in first second (FEV1).
3. Percentage of FVC expelled as FEV1 (FEV1/FVC)

All the patients were subjected to HRCT after getting informed consent.

Serial slices 2 mm in width and 10 mm apart were taken from the apex of the lung to base and reconstructed on a High-resolution bone algorithm. HRCT was done from the Department of Radiology, Govt. Rajaji Hospital, Madurai. Reports were given by qualified Radiologists.

The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2008). Using the software range, frequencies, percentage, mean, standard deviation and p value were calculated. P value of < 0.05 was taken as significant.

RESULTS AND ANALYSIS OF OBSERVED DATA

TABLE 1. SEX DISTRIBUTION AMONG PATIENTS:

Sex	No. of patients	%
Male	10	22.2
Female	35	77.7

In this study out of 45 cases, 35 are females and 10 are males.

The females are 78% and males are 22%. Sex ratio= 3.5:1 (F:M).

TABLE 2: AGE DISTRIBUTION AMONG STUDY POPULATION:

Age group	**FEMALE**	**MALE**	**No. of patients**	**Percentage**
30- 39 years	9	1	10	22.2%
40- 49 years	10	4	14	31.1%
50- 59 years	12	4	16	35.6%
>60 years	4	1	5	11.1%
TOTAL	35	10	45	100%

The age of patients ranges between 32 to 65 years. Mean age was 47.7 years. Most number of cases was from age group of 50-59 years.

TABLE 3: PATTERN OF SYMPTOMS AMONG PATIENTS:

SYMPTOMS	NO. OF PATIENTS	PERCENTAGE
Dry cough	9	20%
Cough with expectoration	3	6.66%
Exertional dyspnoea	21	46.66%
Chest pain	6	13.33%
Dry cough with dyspnoea	9	20%
No symptoms	5	11.11%

Most of the patient had dyspnoea on exertion (47%) as their respiratory symptom. Twenty percent of patients had dry cough.

TABLE 4: DURATION OF DISEASE:

Duration of disease	No. of patients	Percentage
<5 years	9	20%
5- 9 years	23	51%
>10 years	13	29%
TOTAL	45	100%

Eighty percent of patients had history of rheumatoid arthritis for more than five years. Most number of patients had 5- 9 years of disease duration. Mean duration of disease was around 9 years.

TABLE 5: **CLINICAL PARAMETERS:**

PARAMETER	NO. OF PATIENTS	PERCENTAGE
SUB CUTANEOUS NODULES	13	29%
JOINT DEFORMITY	15	33%

RESPIRATORY SIGNS:

CRACKLES	19	42%
WHEEZE	10	22%
NO SIGNS	16	36%

DISEASE ACTIVITY:

RF POSITIVE	35	78%
RF NEGATIVE	10	22%
CRP POSITIVE	37	82%
CRP NEGATIVE	8	18%

Out of 45 patients 13(29%) had subcutaneous nodules on examination and 15(33%) had some kind of joint deformity.

On examination of respiratory system 42% of patients had predominant crepitations.

RF was positive in 78% of cases and CRP was positive in 85% of cases.

TABLE 6: **DISEASE PARAMETERS:**

PARAMETER	**RANGE**	**MEAN**	**S.D.**
Disease duration (yrs)	3- 28	8.93	6.34
Hb %	8.2- 12	10.04	1.15
ESR mm/hr	22- 130	55.97	28.77
DAS 28 score	2.9- 6.51	5.05	0.86

Mean hemoglobin was around 10 g% and mean ESR was around 56 mm/hr.

DAS 28 score ranges between 2.9 to 6.51 with mean value of 5.05 with standard deviation 0.86

TABLE 7: DAS 28 SEVERITY:

SEVERITY	NO. OF PATIENTS	PERCENTAGE
MILD (≤3.1)	3	7%
MODERATE (3.2- 5.1)	24	53%
SEVERE (>5.1)	18	40%

This table shows that 3 out of 45 (7%) had mild disease and 24 patients (53%) had moderate disease. 18 people (40%) had severe disease activity.

TABLE 8: ABNORMAL REPORTS:

Investigation	Abnormal	Normal	Total
Chest X ray	25 (56%)	20 (44%)	45
PFT	25 (56%)	20 (44%)	45
HRCT	32 (71%)	13 (29%)	45

Out of 45 people 25(56%) had chest X ray and pulmonary function test abnormality. 32 patients (71%) had abnormal HRCT findings.

TABLE 9: CHEST X-RAY FINDINGS:

FINDING	NO. OF PATIENTS	PERCENTAGE
Normal	20	44.5%
Increased BVM	14	31%
Opacities	10	22%
Pleural effusion	2	4.5%

Of the total 45 patients, 20(44.5%) had normal chest x ray. 14 patients (31%) had increased bronchovascular markings and 10 had some opacity over the lung parenchyma. Two of them had minimal bilateral pleural effusion.

TABLE 10: CHEST X RAY WITH HRCT FINDINGS:

	HRCT ABNORMAL	HRCT NORMAL	NO.	%
CXR ABNORMAL	18	7	25	56%
CXR NORMAL	14	6	20	44%
	32	13	45	
		P value- 0.84 (not significant)		

Chest X ray was abnormal in 18 out of 32 patients (56%) with HRCT abnormality and it was normal in 14 patients (44%) with HRCT abnormality.

Seven out of 13(54%) patients with normal HRCT had some chest x ray abnormality and Six (46%) patients had normal chest x ray.

TABLE 11: PFT PARAMETERS:

	RANGE	MEAN	S.D.
FVC (Litres)	1.22- 2.74	1.83	0.39
FEV1 (Litres)	0.98- 2.34	1.58	0.35
FVC %	49- 96	77.4	11.9
FEV1 %	53- 101	79.2	11.2
FEV1/FVC %	62- 97	86.4	6.97

Mean FVC % predicted was 77.4%, the range being 49 to 96%.

Mean FEV1/FVC was 86.4%, ranges between 62 to 97%.

TABLE 12: PFT PATTERN WITH DURATION OF DISEASE:

DURATION	NORMAL PFT	ABNORMAL PFT	TOTAL	
< 5 YEARS	7	2	9	P VALUE: 0.04 (Significant)
5- 9 YEARS	10	13	23	
>10 YEARS	3	10	13	
TOTAL	20	25	45	

Seven out of nine (78%) patients with duration of disease < 5 years had normal PFT. Out of 36 patients with disease duration >5 years 26(64%) had abnormal PFT. There is significant relation between duration of disease with PFT abnormality.

TABLE 13: PATTERN OF PFT FINDINGS:

PATTERN	**NO. OF PATIENTS**	**%**
NORMAL	20	45%
RESTRICTIVE	23	51%
OBSTRUCTIVE	2	4%

Out of 25 abnormal PFTs 23(92%) had restrictive pattern. Two out of 25 (8%) had obstructive pattern of PFT abnormality.

TABLE 14: SEVERITY OF RESTRICTIVE PATTERN:

SEVERITY	NO. OF PATIENTS	%
MILD	10	43%
MODERATE	12	52%
SEVERE	1	5%

Twelve out of 23(52%) patients had moderate restrictive pattern, 10(43%) had mild restriction and only one patient had severe restriction on PFT.

Severity of restrictive pattern in pulmonary function test is classified according to percentage of predicted FVC[89, 90].

Mild - 70-79%.

Moderate - 50- 69%

Severe - <50%

TABLE 15: HRCT FINDINGS:

HRCT FINDINGS	NO. OF PATIENTS	%
Reticular pattern	23	71.8
Reticulonodular pattern	8	25
Ground glass opacities	12	38
Nodules	4	12.5
Honey comb pattern	9	28.1
Bronchiectasis	8	25
Peribronchial thickening and cuffing	10	31.25
Pleural effusion	8	25
Pleural thickening	10	31.25

Most of the patients had multiple HRCT findings. 23 out of 32 patients (72%) had reticular pattern in HRCT, followed by ground glass opacities in 12 patients (38%).

Pleural thickening and peribronchial thickening and cuffing were seen in 31.3% of cases.

Honey comb pattern was seen in 28% of cases.

Bronchiectasis was present in 8 (25%) patients.

Pleural effusion was present in 25% of cases.

Pulmonary nodules were seen in only 4(12.5%) cases.

TABLE 16: COMPARISON OF HRCT NORMAL AND HRCT ABNORMAL PATIENTS:

SI NO.	PARAMETER	ABNORMAL HRCT (N= 32)	NORMAL HRCT (N= 13)	TOTAL NO. PATIENT (N= 45)	P VALUE (Chi square test)
1.	Male	8	2	10	P value- 0.75 (Not significant)
	Female	24	11	35	
2.	Duration of disease < 5 years	4	5	9	P value-0.042 (Significant)
	>5 years	28	8	36	
3.	Sub cut. nodules Present	12	1	13	P value-0.042 (Significant)
	Absent	20	12	23	
4.	RF positive	28	7	35	P value-0.03 (Significant)
	RF negative	4	6	10	
5.	CRP positive	27	10	37	P value- 0.08 (Not significant)
	CRP negative	5	3	8	
6.	PFT abnormal	21	4	25	P value-0.043 (Significant)
	PFT normal	11	9	20	

There is no significant difference between males and females in the occurrence of HRCT abnormalities (p value- >0.05). But out of 10 male patients 8 (80%) had HRCT abnormalities in contrast to females, in which 22 out of 35 (69%) had the same.

There is statistically significant relation between the duration of disease. Out of nine patients who had disease duration <5 years, only 4(44%) had HRCT abnormalities. 28 patients out of 36 (78%), who had disease duration >5 years, had HRCT abnormalities.

Those who have subcutaneous nodules have high chance occurrence of HRCT abnormality. Out of 13 patients with subcutaneous nodules 12 (92%) had some HRCT abnormalities.

There is significant relation between Rheumatoid factor positivity and HRCT abnormality. 28 out of 32 (88%) patients with HRCT findings had RF positivity. Only 7 out of 13 (54%) patients with normal HRCT had RF positivity.

There is no significant relation between CRP positivity and HRCT findings. 84% (27/32) of HRCT abnormal patients had CRP positivity and 77% (10/13) of patients with normal HRCT also had CRP positivity.

There was significant association between HRCT and PFT findings. 21 out of 32 patients (66%) with HRCT findings have PFT abnormalities. Nine out of 13 (69%) patients with normal HRCT have normal PFT. 34% of HRCT abnormal patients show a normal PFT pattern and 31% of HRCT normal patients show an abnormal PFT.

Specificity and sensitivity calculated in comparison with HRCT finding were 69% and 66% respectively. Positive predictive value of PFT was 84% and negative predictive value of PFT was only 45%.

DISCUSSION

Rheumatoid arthritis (RA) is a chronic multi-system disease of unknown cause. It is a systemic inflammatory disease and affects 1-2% of the general

population. A major portion of morbidity and mortality are due to RA are due to its extra-articular manifestations. A variety of pulmonary manifestations are associated with RA and lung disease is the second most common cause of death (18%) after infection (27%) in patients with RA[91].

In our study, we selected 45 patients from Rheumatology clinic, Govt. Rajaji Hospital, Madurai, who are already diagnosed to have Rheumatoid arthritis as per American Rheumatism Association guidelines. We selected those patients who have either respiratory symptoms or signs.

The sex distribution in this study, predominantly affects females in the ratio of 3.5:1. According to Harrison 17th edition, API text book of medicine, the females are affected 3 times more than males. In this study males are 22% and females are 78%. Doran MF, Ponal et al study, males are 26.9% and females are 73.1%[92]. In a study conducted by Raniga S, Sharma P et al in 2006, the female to male ratio was 3:1[93]. There were 23.3% males and 76.7% females.

The mean age in our study is 47.7 years. Most number of cases in between 50- 59 years (35.6%). In a study conducted by Raniga et al, average age of male patients was 48.4 years and for females 45.8 years[93]. The average age of patients in our study was comparable to that of other studies. The mean age of onset of lung disease was in the fifth or sixth decade.

In this study, average duration of rheumatoid arthritis is 8.9 ± 6.3 years.

Most number of patients is in between 5- 9 years of age (51%). In a study by Tanaka et al on rheumatoid arthritis related lung diseases average duration of disease was 7.6 ± 9.2 years[94]. In a study conducted by Stephen C Morrison et al, average duration of disease was 12.4 years[95]. In a study by R Prasad et al[99] the mean age of study group were 52.6 years (Range 18-66) and the mean duration of rheumatoid arthritis was 11.9 years.

In this study, predominant respiratory symptom is dyspnoea, which was present in 30 patients out of 45 (67%), followed by dry cough in 40% (18 out of 45) patients. In a study by G S Gaude et al also the most common symptom was dyspnoea in 57% of patients (68 out of 119), followed by dry cough (59 out of 119)[96].

In our study, 12 out of 13 patients (92%) with rheumatoid nodule are RF positive. Rheumatoid nodules are more common in males than in females and are closely associated with RF seropositivity[98]. But in our study, only four out of 13 patients (31%) with subcutaneous nodules are males.

Patients with rheumatoid nodules were more likely to have lung involvement. In our study population, 12 patients with rheumatoid nodule had HRCT findings and only one patient with nodule had normal HRCT. In S Raniga et al study, three patients with rheumatoid nodules had HRCT findings consistent with ILD and no patient without lung involvement had rheumatoid nodule[93].

In our study respiratory signs in the form of crackles or wheeze were present in 64% of patients, in contrast to Raniga et al study where, that was present in only 10% of patients. This may be due to the fact that we included only symptomatic cases in our study, but Raniga et al study included all rheumatoid patients irrespective of respiratory symptoms.

In our study RF is positive in 78% (35 out of 45) of cases and there is high correlation between RF positivity and pulmonary manifestations. In Raniga et al study, RF was positive in 83.3% of cases[93].

Müller- Leisse C et al, in his study states that RA with HRCT findings were associated with higher level of RF and there was no

relationship between pulmonary changes and either the duration of the disease, antinuclear antibodies (ANA) or C-reactive protein[97]. In our study 82% of patients are CRP positive. But there is no significant relation between HRCT findings and CRP positivity.

In our study average DAS 28 score is 5.05±0.86, most of the patients are in moderate severity (score between 3.2- 5.1). 24 out of 45 patients (53%) are of moderate disease activity. 40% of patients have severe disease activity according to DAS 28. Toshihisomatsui et al[100] in their study reported 11.6% patients had mild disease, 51.4% had moderate DAS score and 45.5 % of patients had severe disease activity. In our study there is no significant correlation between DAS28 severity and HRCT findings.

In our study, 25 out of 45 patients (56%) show abnormal chest x ray. 18 patients out of 32 (56%) with HRCT findings show abnormal x ray and 14 out of 32 patients (44%) with HRCT findings have normal chest x ray. Seven out of 13 patients (54%) with normal HRCT have x ray abnormalities. Sensitivity and specificity of chest x ray in detecting pulmonary manifestations, with respect to HRCT are 56% and 46% respectively. Most of the patients with abnormal x ray shows increased bronchovascular markings (14 out of 25), which is highly nonspecific. 10

patients (40%) show reticular and reticulonodular opacities suggestive of ILD. Two patients have minimal pleural effusion in the x ray.

In this study, 25 out of 45 (56%) patients show abnormal PFT. PFT findings has got positive correlation with the duration of disease in this study.23 out of 36 (64%) patients with duration >5 years show PFT changes. 22% (two out of nine) of patients with duration <5 yrs show PFT changes.

21 out of 32 (66%) patients with abnormal HRCT have abnormal PFT. 11 out of 32 patients (34%) with abnormal HRCT have normal PFT. Out of normal HRCT patients 69% of patients have normal PFT. Sensitivity and specificity of PFT are 66% and 69% respectively in our study. Out of 25 patients with abnormal PFT, 23 (92%) have restrictive pattern, 2 patients show obstructive pattern. Of the restrictive patients, 10 (44%) show mild restriction, 8 (38%) have moderate restriction and 4 patients show severe restriction. 2 cases of obstructive pattern are associated with bronchiectasis in HRCT.

Mean FVC is 1.83L ±0.39. Average percentage predicted FVC is 77.4 ± 12%. Mean FEV1/FVC is 86.4 ±6.97%.

In the study conducted by Raniga et al, abnormalities detectable on chest radiograph were 13.33%. Chest x-ray showed changes consistent with ILD in 4/30 (13.3%) including bilateral reticular infiltrates in three

and honeycombing in one and x-ray chest was normal in 7/11 (63.6%) patients with HRCT positive ILD. Chest radiograph is the least sensitive with only four out of thirty patients shows findings consistent with interstitial disease. In our study, the ability of PFTs to pick up an abnormality was better than the chest radiographs which were 66% and 56% respectively.

In a study conducted by McDonagh et al[103], spirometric abnormalities were noted in 8/30 (26.6%) and radiological abnormality in13%. In the same study, HRCT findings consistent with ILD were seen in eleven out of thirty patients (36%), compared to the spirometric findings in 8/30 (26.6%). The results of HRCT have not been shown to correlate with pulmonary function tests. But in our study there is significant correlation between HRCT and PFT results.

In a study conducted by R Prasad et al, spirometry showed restrictive pattern in 52.9 % cases (Mean FEV1/FVC 86 % and Mean FVC 1.16 Litre) and obstructive pattern noted in 11.8 % while 6 (35.3 %) patients did not cooperate[99].

In a study conducted by Cervantes-Perez et al, no correlation was found between the disease duration, the number of patients and the severity of restrictive PFT abnormality[101]. But in our study there is a positive correlation between duration and PFT changes. This may be due

to very less number of patients (9 out of 45) who have disease duration <5 years and mean duration of disease is 9 years. We haven't screened asymptomatic subjects, who are in the early stages of the disease. In our study we have positive correlation between HRCT findings and duration of disease also.

In G S Gaude et al study, pulmonary functions were abnormal in almost 89% of the patients with RA and the most common defect in these patients was restrictive defect (79%). HRCT shows evidence of interstitial lung disease in 11 out of 30 patients and so the most sensitive of all parameters[96]

The HRCT study by Fewins et al of patients with RA revealed a high prevalence of ILD (44%) with maximum patients having mild restriction and lesser patients having moderate and severe restriction[102].

In our study 32 patients out of 45(71%) have abnormal HRCT. Out of 32, there are 8 males and 24 females. There is no significant difference between male and female in occurrence of HRCT abnormality. But, out of 10 males, 8 (80%) have HRCT findings and out of 35 females, 24 (69%) have the same.

The pleuropulmonary manifestations of RA are seen more commonly in men than women[105].

The spectrum of RA-associated lung is extremely broad. A multiplicity of CT patterns is commonly seen in patients with rheumatoid arthritis. The ILD is the most common manifestation of RA[106.] Finding consistent with Interstitial Lung disease (ILD) was defined as the presence of GGO, IPF (reticular pattern, honeycombing), traction bronchiectasis, or interlobular septal thickening. High resolution computed tomography is a more sensitive method of detecting ILD and pleural effusion.

The HRCT study by Fewins et al[102] of patients with RA revealed a high prevalence of ILD (44%). In Raniga et al study, prevalence of ILD is 36%[93].

In our study, of the 32 cases with HRCT findings, 72% have reticular pattern (23/32 patients), followed by ground glass pattern which comes around 38% (12 cases). Honeycombing is seen in 9 patients (28%). Tractional bronchiectasis is present in 25% of cases.28 out of 32 HRCT findings are consistent with the presence of ILD (88%).

Pleural involvement in the form of pleural effusion (25%) and pleural thickening (31%) are observed. Isolated pleural involvement is rare and is present in 2 cases (6%). Pulmonary nodules are seen in 4 cases (13%). Almost all cases with ground glass opacities occur along with reticular pattern or honeycomb pattern.

In BIEDERER J et al study[104], in 49 of 53 patients, HRCT was suggestive of ILD associated with RA. Reticular lesions were found in 40 of 53 patients, in 15 of 40 presenting as mixed pattern with ground-glass opacities (GGO). Pure reticular patterns predominated in patients with long duration of ILD. Pure GGO were not observed.

In the Gaude et al study[96], Reticular, nodular and the combined pattern were observed in the majority of the cases (58.9%). Interstitial pattern consistent with ILD was observed in 44.5% of the patients. The common abnormality observed was reticulonodular lesions on HRCT of the thorax. Pleural effusions were observed in 8% of the cases and bronchiectasis was observed in 5% of the patients with RA. Bronchiectasis has been reported in as many as 30% of patients with RA undergoing HRCT.

In Müller- Leisse C et al study[97], 58 patients (70%) had pathological CT scans showing the following abnormalities: interlobular thickening (44.5%), intralobular thickening (34%), nonseptal linear attenuation (35%), nodular or linear pleural thickening (32.5%), ground-glass pattern (19%), centrilobular nodules (13%), honeycombing (13%) and bronchiectasis (9%).

In Tanaka et al study[94], ground glass opacity (57 [90%] patients) and reticulation (62 [98%] patients) were the most common CT features. Four major CT patterns were identified: usual interstitial pneumonia (n=26), nonspecific interstitial pneumonia (n=19), bronchiolitis (n= 11), and organizing pneumonia (n=5). Usual interstitial pneumonia and nonspecific interstitial pneumonia CT patterns overlapped; GGO was more extensive in patients with nonspecific interstitial pneumonia CT pattern.

CONCLUSION

1. Sex ratio of female to male in this study is 3.5:1
2. Most of the patients are distributed between 50- 59 years.
3. Dyspnoea on exertion is the most common respiratory symptom.
4. 80% of patients have history of Rheumatoid arthritis for more than 5 years. Average duration of disease is 9 years.
5. Rheumatoid factor is positive among 78% of cases. There is high correlation between RF positivity and lung involvement.
6. 92% of patients with subcutaneous nodule are RF positive. Patients with subcutaneous nodules are more likely to have lung manifestations.
7. PFT and HRCT findings have positive correlation. Mild restrictive pattern is the most common abnormal PFT pattern.
8. PFT and HRCT abnormalities have got positive correlation with duration of disease.
9. HRCT is the most sensitive modality to detect lung involvement in rheumatoid arthritis. HRCT can show evidence of ILD even when PFT parameters and chest radiograph are normal.
10. ILD is the most common pulmonary manifestation (88%) in Rheumatoid arthritis in the form of reticular and ground glass pattern in HRCT.

SUMMARY

The study "Pulmonary manifestations of Rheumatoid arthritis" is a descriptive study conducted on patients attending Rheumatology outpatient department, Govt. Rajaji Hospital, Madurai. Forty five patients of Rheumatoid arthritis with either respiratory symptoms or signs are included in the study. Selected patients underwent clinical, laboratory investigations, pulmonary function test, chest x ray and HRCT to detect pulmonary involvement.

The information collected regarding all cases were recorded in a master chart and data analysis done with the help of Epidemiological Information Package (EPI 2008).

Analyzing the data shows sex ratio among study population of 3.5:1 with female predominance. 50- 59 years of age is most commonly involved. 80% of patients are with duration of disease more than 5 years. Most common respiratory symptom is dyspnoea. 78% of patients are rheumatoid factor positive. There is high correlation between lung involvement and RF positivity. 92% of patients with subcutaneous nodules are RF positive. Patients with nodules are more likely to develop lung manifestations. Restrictive pattern is the commonest PFT finding. PFT and HRCT have got positive correlation. HRCT is the most sensitive modality to detect lung involvement. ILD is the most common pulmonary manifestation of Rheumatoid arthritis in the form of reticular pattern in HRCT.

GLOSSARY

RA	-	Rheumatoid arthritis
RF	-	Rheumatoid factor
CRP	-	C reactive protein
ESR	-	Erythrocyte sedimentation rate
Hb	-	Hemoglobin
DAS	-	Disease activity score
Anti CCP	-	Anti cyclic citrullinated protein
DMARD	-	Disease modifying anti rheumatic drugs
PFT	-	Pulmonary function test
HRCT	-	High resolution computed tomography
FVC	-	Forced vital capacity
FEV1	-	Forced expiratory volume in first one second
FEF	-	Forced expiratory flow
ILD	-	Interstitial lung disease
IPF	-	Idiopathic pulmonary fibrosis
GGO	-	Ground glass opacity
UIP	-	Usual interstitial pneumonia
NSIP	-	Nonspecific interstitial pneumonia

BIBLIOGRAPHY

1. Arnett FC, Edworthy SM, Bloch DA et al .The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31:315-324.

2. PETER E LIPSKY : Harrisons Principle of Internal Medicine, 17th edition, McGraw Hill, vol 2: page 2083- 2092.

3. Copemans text book of rheumatic diseases, vol 1.

4. Davidson's Principles and Practice of Medicine, 21st edition.

5. Principles and practice of medicine- Harvey and Jones.

6. Wolfe F, Mitchell DM, Sibley JT, *et al* (April 1994). "The mortality of rheumatoid arthritis". *Arthritis Rheum.* **37** (4): 481–94.

7. Aviña-Zubieta JA, Choi HK, Sadatsafavi M *et al* (Dec 2008). "Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies". *Arthritis Rheum.* **59** (12): 1690–1697.

8. Gupta A and Fomberstein B (August 2009). "Evaluating cardiovascular risk in rheumatoid arthritis". *Journal of Musculoskeletal Medicine* **26** (8): 481–94.

9. E A Kim, K S Lee; T Johkoh et al ; ILD in association with radiological and histological features. Radiographics Oct 1, 2002. 151-165.

10. Citation: H. Rehman : Hemolytic Anemia following Mycoplasma Infection. The Internet Journal of Hematology.2008 Volume 4 Number1.

11. Westwood OM, Nelson PN, Hay FC (April 2006). "Rheumatoid factors: what's new?". *Rheumatology (Oxford)* **45** (4): 379–85

12. Nishimura K, Sugiyama D, Kogata Y, *et al* (June 2007). "Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis" (PDF). *Ann. Intern. Med.* **146** (11): 797–808.

13.Renger F, Bang H, Fredenhagen G, Natusch A, Backhaus M, Feist E, Egerer K, Burmester GR. "Anti-MCV Antibody Test for the Diagnosis of Rheumatoid Arthritis Using a POCT-Immunoassay". *American College of Rheumatology, 2008 Annual Scientific Meeting, poster presentation*.

14. Luime JJ, Colin EM, Hazes JM, Lubberts E. (2009). "Does anti-MCV has additional value as serological marker in the diagnostic and prognostic work-up of patients with rheumatoid arthritis? A systematic review.". *Ann Rheum Dis. 2009 Mar 15*.

15. Schueller-Weidekamm C. Modern ultrasound methods yield stronger arthritis work-up. Diagnostic Imaging. May 2010:20-22.

16. Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Ghogomu E, Tugwell P. Biologics for

rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2009, Issue 4.

17. Edwards J, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close D, Stevens R, Shaw T (2004). "Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis.". *N Engl J Med* **350** (25).

18. Vital E, Emery P (Sep 15 2005). "Advances in the treatment of early rheumatoid arthritis.". *Am Fam Physician* **72** (6): 1002, 1004.

19."Combination therapy in rheumatoid arthritis". Retrieved 2010-07-22.

20."Hypersensitivity reactions". Retrieved 2008-09-20.

21. Walters MN, Ojeda VJ. Pleuropulmonary necrobiotic rheumatoid nodules. A review and clinicopathological study of six patients. *Med J Aust* 1986;144:648–651.

22. Caplan A. Certain unusual radiographic appearances in the chest of coal-miners suffering from rheumatoid arthritis.*Thorax* 1953;8:19–37.

23**.** Alvarez-Lafuente R, Fernández-Gutiérrez B, de Miguel S, *et al* (September 2005)."Potential relationship between herpes viruses and rheumatoid arthritis: analysis with quantitative real time polymerase chain reaction". *Ann. Rheum. Dis.* 64 .

24. Ferrell PB, Aitcheson CT, Pearson GR, Tan EM (March 1981)."Seroepidemiological study of relationships between Epstein-Barr virus and rheumatoid arthritis". *J. Clin. Invest.* **67** .

25. Catalano MA, Carson DA, Slovin SF, Richman DD, Vaughan JH (November 1979)."Antibodies to Epstein-Barr virus-determined antigens in normal subjects and in patients with seropositive rheumatoid arthritis". *Proc. Natl. Acad. Sci. U.S.A*

26. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther 2009;11(3):229

27. Spector TD. Rheumatoid arthritis. Rheum Dis Clin North Am 1990; 16(3):513–37.

28. Mori S, Cho I, Koga Y, et al. A simultaneous onset of organizing pneumonia and rheumatoid arthritis, along with a review of the literature. Mod Rheumatol 2008; 18(1):60–6.

29. Nannini C, Ryu JH, Matteson EL. Lung disease in rheumatoid arthritis. Curr Opin Rheumatol 2008; 20(3):340–6.

30.Saag KG, Kolluri S, Koehnke RK, et al. Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities. Arthritis Rheum 1996;39(10):1711–9.

31. Byrd SL, Case BA, Boulware DW. Pulmonary manifestations of rheumatic disease. Postgrad Med 1993;93:149–51, 154–6, 159–61

32. Boulware DW, Weissman DN, Doll NJ. Pulmonary manifestations of the rheumatic diseases. Clin Rev Allergy 1985;3:249–67.

33. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis* 2003;62:722–727

34. Suzuki A, Ohosone Y, Obana M, Mita S, Matsuoka Y, Irimajiri S, Fukuda J. Cause of death in 81 autopsied patients with rheumatoid arthritis. *J Rheumatol* 1994;21:33–36.

35. Zrour SH, Touzi M, Bejia I, Golli M, Rouatbi N, Sakly N, Younes M, Tabka Z, Bergaoui N. Correlations between high-resolution computed tomography of the chest and clinical function in patients with rheumatoid arthritis: prospective study in 75 patients.*Joint Bone Spin* 2005;72:41–47.

36.Bilgici A, Ulusoy H, Kuru O, Celenk C, Unsal M, Danaci M. Pulmonary involvement in rheumatoid arthritis.*Rheumatol Int* 2005;25:429–435.

37. Lee HK, Kim DS, Yoo B, Seo JB, Rho JY, Colby TV, Kitaichi M. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. *Chest* 2005;127:2019–2027

38. Weyand CM, Schmidt D, Wagner U, Goronzy JJ. The influence of sex on the phenotype of rheumatoid arthritis.*Arthritis Rheum* 1998;41:817–822.

39. Vessey MP, Villard-Mackintosh L, Yeates D. Oral contraceptives, cigarette smoking and other factors in relation to arthritis. *Contraception* 1987;35:457–464

40. Harrison BJ. Influence of cigarette smoking on disease outcome in rheumatoid arthritis. *Curr Opin Rheumatol*2002;14:246–252.

41.Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, Ronnelid J, Harris HE, Ulfgren AK, Rantapaa-Dahlqvist S, *et al*. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum*2006;54:38–46.

42. Manfredsdottir VF, Vikingsdottir T, Jonsson T, Geirsson AJ, Kjartansson O, Heimisdottir M, Sigurdardottir SL, Valdimarsson H, Vikingsson A. The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis. *Rheumatology (Oxford)* 2006;45:734–740.

43. Luukkainen R, Saltyshev M, Pakkasela R, Nordqvist E, Huhtala H, Hakala M. Relationship of rheumatoid factor to lung diffusion capacity in

smoking and non-smoking patients with rheumatoid arthritis. *Scand J Rheumatol*1995;24:119–120

44. Selman M, Pardo A, Barrera L, Estrada A, Watson SR, Wilson K, Aziz N, Kaminski N, Zlotnik A. Gene expression profiles distinguish idiopathic pulmonary fibrosis from hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2006;173:188–198.

45.Vourlekis JS, Schwarz MI, Cherniack RM, Curran-Everett D, Cool CD, Tuder RM, King TE Jr, Brown KK. The effect of pulmonary fibrosis on survival in patients with hypersensitivity pneumonitis. *Am J Med*2004;116:662–668.

46. Collard HR, Cool CD, Leslie KO, Curran-Everett D, Groshong S, Brown KK. Organizing pneumonia and lymphoplasmacytic inflammation predict treatment response in idiopathic pulmonary fibrosis. *Histopathology* 2007;50:258–265.

47. Vassallo R, Matteson E, Thomas CF Jr. Clinical response of rheumatoid arthritis-associated pulmonary fibrosis to tumor necrosis factor-alpha inhibition. *Chest* 2002;122:1093–1096

48. Peno-Green L, Lluberas G, Kingsley T, Brantley S. Lung injury linked to etanercept therapy. *Chest*2002;122:1858–1860

49. Miyagawa Y, Nagata N, Nakanishi Y, Aizawa H, Satake M, Hayashi S, Yagawa Y. A case of steroid-responsive organizing pneumonia in a

patient with rheumatoid arthritis showing migratory infiltration and normal glucose levels in pleural effusions. *Br J Rheumatol* 1993;32:829–831.

50. Chang HK, Park W, Ryu DS. Successful treatment of progressive rheumatoid interstitial lung disease with cyclosporine: a case report. *J Korean Med Sci* 2002;17:270–273

51. Cambridge G, Stohl W, Leandro MJ, Migone TS, Hilbert DM, Edwards JC. Circulating levels of B lymphocyte stimulator in patients with rheumatoid arthritis following rituximab treatment: relationships with B cell depletion, circulating antibodies, and clinical relapse. *Arthritis Rheum* 2006;54:723–732

52. Kelly C, Saravanan V. Treatment strategies for a rheumatoid arthritis patient with interstitial lung disease. Expert Opin Pharmacother 2008;9(18): 3221–30.

53. Saketkoo LA, Espinoza LR. Experience of mycophenolate mofetil in 10 patients with autoimmune-related interstitial lung disease demonstrates promising effects. Am J Med Sci 2009;337(5):329–35.

54. Joseph J, Sahn SA. Connective tissue diseases and the pleura. *Chest* 1993;104:262–270

55. Helmers R, Galvin J, Hunninghake GW. Pulmonary manifestations associated with rheumatoid arthritis. *Chest*1991;100:235–239.

56. Gary S. Rheumatoid arthritis. In: Kelley WN, editor. Textbook of rheumatology. Vol 2. 5th ed. Philadelphia: WB Saunders; 1997:851–8.

57. Vergnenegre A, Pugnere N, Antonini MT, Arnaud M, Melloni B, Treves R, Bonnaud F. Airway obstruction and rheumatoid arthritis. *Eur Respir J* 1997;10:1072–1078.

58. Remy-Jardin M, Remy J, Cortet B, Mauri F, Delcambre B. Lung changes in rheumatoid arthritis: CT findings.*Radiology* 1994;193

59. Perez T, Remy-Jardin M, Cortet B. Airways involvement in rheumatoid arthritis: clinical, functional and HRCT findings. *Am J Respir Crit Care Med* 1998;157:1658–1665

60. Homma S, Kawabata M, Kishi K, Tsuboi E, Narui K, Nakatani T, Uekusa T, Saiki S, Nakata K. Diffuse panbronchiolitis in rheumatoid arthritis. *Eur Respir J* 1998;12:444–452

61. White ES, Tazelaar HD, Lynch JP 3rd. Bronchiolar complications of connective tissue diseases. Semin Respir Crit Care Med 2003;24:543–66.

62. Schwarz MI, Zamora MR, Hodges TN, et al. Isolated pulmonary capillaritis and diffuse alveolar hemorrhage in rheumatoid arthritis and mixed connective tissue disease. Chest 1998;113(6): 1609–15.

63. Kremer JM, Alarcon GS, Weinblatt ME, et al. Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated

lung injury in patients with rheumatoid arthritis: a multicenter study with literature review. Arthritis Rheum 1997; 40(10):1829–37

64. Cannon GW. Methotrexate pulmonary toxicity. Rheum Dis Clin North Am 1997;23(4):917–37.

65. Schnabel A, Dalhoff K, Bauerfeind S, et al. Sustained cough in methotrexate therapy for rheumatoid arthritis. Clin Rheumatol 1996;15(3):277–82.

66. Imokawa S, Colby TV, Leslie KO, et al. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J 2000;15(2):373–81.

67. Tanoue LT. Pulmonary manifestations of rheumatoid arthritis. Clin Chest Med 1998;19(4):667–85.

68. Remy-Jardin M, Remy J, Cortet B, et al. Lung changes in rheumatoid arthritis: CT findings. Radiology 1994;193(2):375–82.

69. McMahon MJ, Swinson DR, Shettar S, et al. Bronchiectasis and rheumatoid arthritis: a clinical study. Ann Rheum Dis 1993;52:776–9.

70. Toussirot E, Despaux J, Wendling D. Increased frequency of HLA-DRB1*0401 in patients with RA and bronchiectasis. Ann Rheum Dis 2000;59(12): 1002–3.

71. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* 1999;159:179-187.

72. LUNGFUNKTION - Practice compendium for semester 6. Department of Medical Sciences, Clinical Physiology, Academic Hospital, Uppsala, Sweden. Retrieved 2010.

73. Interpretation model - compendium at Uppsala Academic Hospital. By H. Hedenström. 2009-02-04.

74. Aaron SD, Dales RE, Cardinal P. How accurate is spirometry at predicting restrictive pulmonary impairment? Chest. 1999, 115: 869-873.

75. Wanger J. Single-breath carbon monoxide diffusing capacity. In: Wanger J. Pulmonary Function Testing: A Practical Approach.2nd edition. Baltimore: Williams & Wilkins, 1996:145–173.

76. Hyatt RE, Scanlon PD, Nakamura M**.** Diffusing capacity of the lungs. In: Hyatt RE, Scanlon PD, Nakamura M. Interpretation of Pulmonary Function Tests: A Practical Guide. Philadelphia: Lippincott-Raven, 1997:41–49.

77. Frank ST, Weg JG, Harkleroad LE, et al. Pulmonary dysfunction in rheumatoid disease. Chest 1973; 63(1):27–34.

78. Chetta A, Aiello M, Foresi A, et al. Relationship between outcome measures of six-minute walk test and baseline lung function in patients

with interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis 2001;18(2):170–5.

79. O'Donnell D. Physiology of interstitial lung disease. In: Schwartz M, editor. Interstitial lung disease. Ontario: BC Decker; 2003. p. 54–74.

80. Dawson et al: fibrosing alveolitis in rheumatoid arthritis patients as detected by HRCT, Chest X Ray, and pulmonary function test.

81. Lamblin C, Bergoin C, Saelens T and Wallaert B. Interstitial lung diseases in collagen vascular diseases. Eur Respir J 2001; 18:69S-80S.

82. Wells AU, Rubens MB, du Bois RM, et al. Serial CT in fibrosing alveolitis: Prognostic significance of the initial pattern. Am J Roentgenol 1993;161:1159-1165

83. Dawson JK, Fewins HE, Desmond J, et al. Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis. Ann Rheum Dis 2002;61(6):517–21.

84. Nagasawa Y, Takada T, Shimizu T, et al. Inflammatory cells in lung disease associated with rheumatoid arthritis. Intern Med 2009;48(14):1209–17.

85. Costabel U, Guzman J, Bonella F, et al. Bronchoalveolar lavage in other interstitial lung diseases. Semin Respir Crit Care Med 2007;28(5):514–24.

86. Kim DS. Interstitial lung disease in rheumatoid arthritis: recent advances. Curr Opin Pulm Med 2006;12(5):346–53.

87. Leslie KO, Trahan S, Gruden J. Pulmonary pathology of the rheumatic diseases. Semin Respir Crit Care Med 2007;28(4):369–78.

88. Kligerman SJ, Groshong S, Brown KK, et al. Nonspecific interstitial pneumonia: radiologic, clinical, and pathologic considerations. Radiographics 2009;29(1):73–87.

89. Barreirdo (2004) Am Fam Physician 69:1107-14.

90.Salzman (1999) J Respir Dis 20:809-22.

91. Boers M, Dijkmans B, Gabriel S, Maradit-Kremers H, O'Dell J, Pincus T.(2004) “Making an impact on mortality in rheumatoid arthritis”. Arthritis Rheum 50:1734–9.

92. Doran M. F, Ponal Gr, Crowson CS, mayo clinic, arthritis Rheum.2002, Mar 46, 625- 635.

93. Raniga S, Sharma P, Kaur G, Arora A, Khalasi Y, Vohra PV. “Interstitial Lung disease in Rheumatoid arthritis "- a study of thirty cases.2006;16(4):835-39.

94. Tanaka et al- rheumatoid arthritis related lung diseases- CT findings, vol 232, number 1, Radiology journal JULY 2004.

95. The lungs in rheumatoid arthritis - a clinical, radiographic and pulmonary function study, Stephen C. Morrison, Girish M. Mody, Sally R. Benatar, Or1ando L Meyers, S *AI, Med* J 1996; 86: 829-833.

96. G.S. Gaude, V. Mahishale and A. Srivastva, Pulmonary Manifestations in Connective Tissue Disorders The Indian Journal of Chest Diseases & Allied Sciences, 2009;Vol.51

97. Pulmonary manifestations in rheumatoid arthritis: high-resolution computed tomography in correlation with the skeletal changes and the laboratory chemical changes, Müller-Leisse C, Bussmann A, Meyer O, Vorbrüggen W, Genth E, Günther RW, Ref. 1996 Nov;165(5):438-44.

98. Kaye BR, Kaye RL, Bobrove A. Rheumatoid nodules. Review of the spectrum of associated conditions and proposal of a new classification, with a report of four seronegative cases. Am J Med 1984; 76(2):279–92.

99. R. Prasad, S. Kant, R. Garg, S. K. Verma, Sanjay & S. Das : Pleuropulmonary manifestations in rheumatoid arthritis . *The Internet Journal of Pulmonary Medicine.* 2007 Volume 8 Number 2.

100. Toshihisomatsui, Yoshali et al, annuals of rheumatic disease 2007:60: 1221-1226.

101. Cervantes-Perez C, Toro-Perez AH, Rodriguez-Jurado-P: "Pulmonary involvement in rheumatoid arthritis".JAMA 243:1715-1719,1980.

102. Fewins HE, McGowan I et al. “HRCT in rheumatoid arthritis associated pulmonary disease”. Br J Rheumatol.1991; 30(3)214-6.

103. McDonagh J, Greaves M, Wright AR, Heycock C, Owen JP, Kelly C. “High resolution computed tomography of the lungs in patients with rheumatoid arthritis and interstitial lung disease”. Br J Rheumatol 1994; 33: 118122.

104. Biederer J, Schnabel A, Muhle C, Gross WL, Heller M, Reuter M. “Correlation between HRCT findings, pulmonary function tests and bronchoalveolar lavage cytology in interstitial lung disease associated with rheumatoid arthritis”. Eur Radiol 2004; 14:272–280.

105. Tanoue LT. Pulmonary manifestations of rheumatoid arthritis. *Clin Chest Med* 1998; 19:667-85.

106. Walker WC, Wrightt V. Pulmonary lesions and rheumatoid arthritis. *Medicine* 1982; 58: 187-9.

PROFORMA

NAME:

AGE: SEX:

OP NO:
ADDRESS:

PHONE NO:

HISTORY:

Arthritis:

Nodules:

Raynaud's phenomenon:

Sicca symptoms:

Cough/expectoration/dyspnoea/chest pain:

Fever:

Muscle weakness- proximal/distal/neck/trunk

PAST HISTORY:

DM/HT/TB/ATT/CAD

PERSONAL HISTORY:

Smoking/Alcohol/ exposure to STD

FAMILY HISTORY:

DM/HT/CAD/Rheumatic diseases

Systemic examination:

RS:

ABDOMEN:

EYE:

Scleritis/episcleritis:

Dry eyes:

No. of tender joints:
No. of swollen joints:

DAS 28 score:

Deformity:

CVS:

CNS:

INVESTIGATIONS:

HEMATOLOGY:

RFT:

B.Sugar:

Hb: B.UREA:

S.cholesterol:

TC: S.Cr:

DC: S.Electrolytes:

ESR:

LFT:

RF:

CRP:

X-RAY Chest:

PFT:

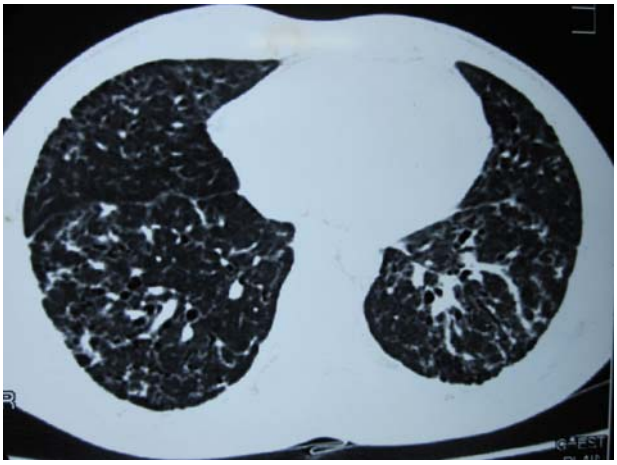
	PATIENT VALUE	PREDICTED VALUE	PERCENTAGE
FVC			
FEV1			
FEV1/FVC			

IMPRESSION:

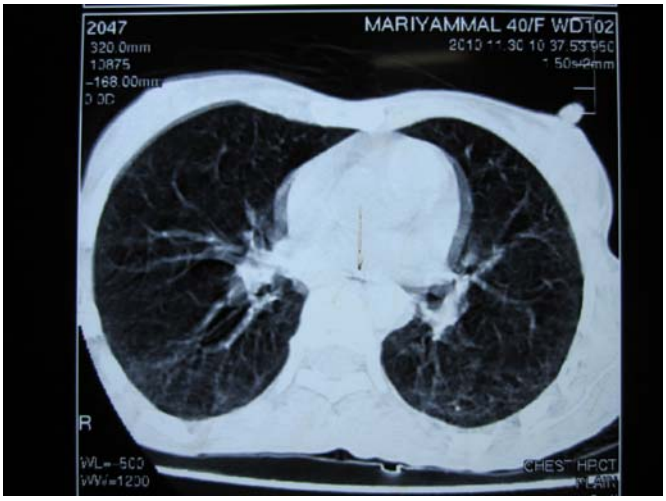
HRCT CHEST:

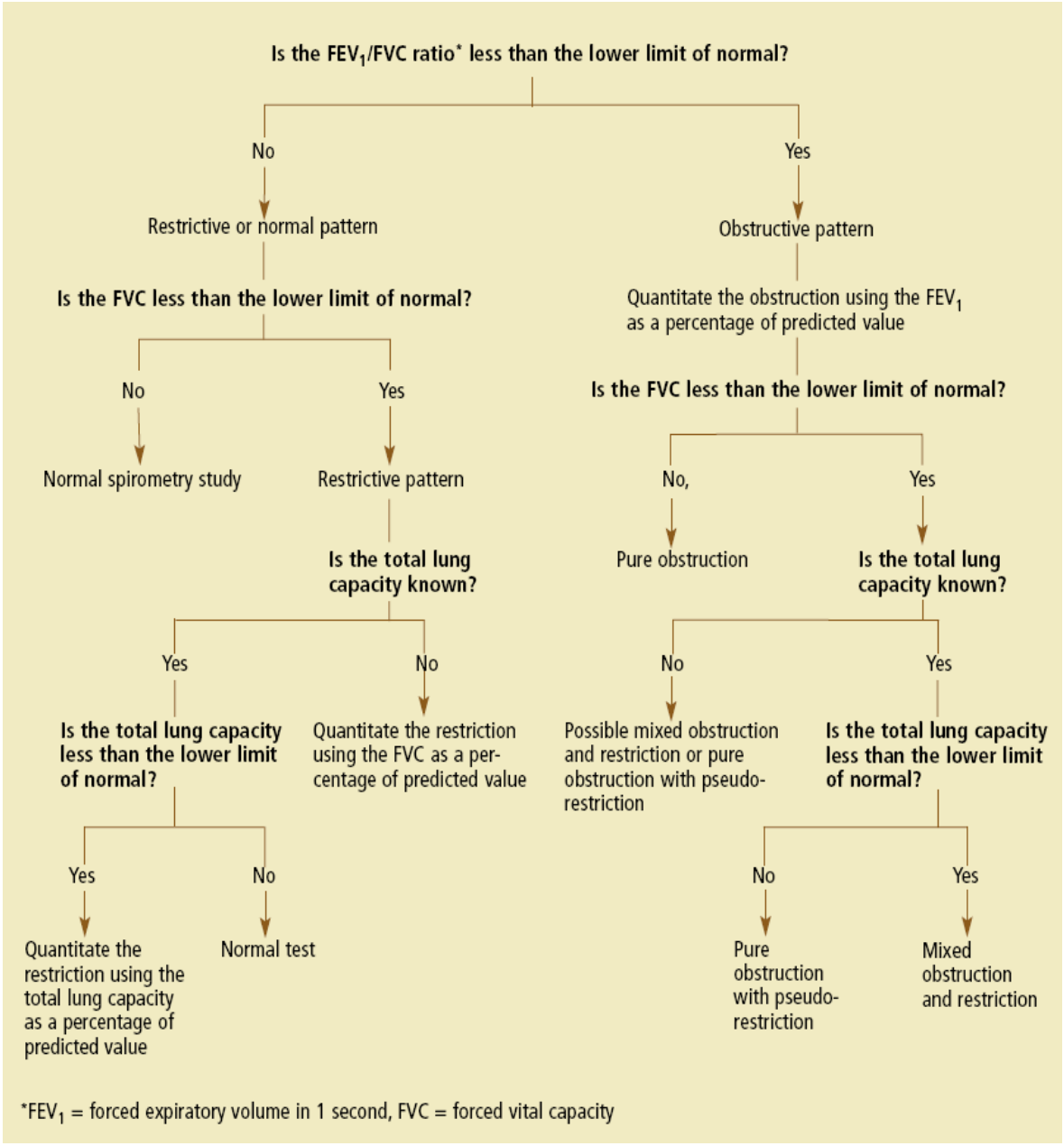
HRCT showing Peribronchial thickening with

ground glass opacity and tractional bronchiectasis



HRCT showing Reticular pattern of opacities





*FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity

serial no.	NAME	age	sex	duration	cough	sputum	dyspnoea	c. pain	s/c nodule	deformity	crepts	wheeze	Hb	ESR	RF	CRP	DAS 28	Chest X ray	x- BVM↑	haziness	x-pl eff	CT-retic	ret-nod	gr. Glass	nodules	hon comb	broectasis	peribro th	pl effn	pl thickn	FVC	FEV1	FVC %	FEV1 %	FEV1/FVC	PFT	
1	VATSALA	52	F	3	N	N	Y	N	N	Y	Y	N	8.2	40	+	+	4.77	Y	N	Y	N	Y	N	Y	N	N	N	N	N	Y	1.24	1.15	59	62	93	RES	
2	RAJAMANI	60	F	6	N	N	Y	Y	N	N	Y	N	11	55	+	+	6.51	N	N	N	N	Y	N	Y	N	Y	N	N	N	N	1.66	1.36	69	68	82	RES	
3	SIVANACHIAR	55	F	4	Y	N	Y	N	N	N	Y	N	9.6	68	+	+	5.78	Y	Y	N	N	Y	N	N	N	N	N	Y	Y	N	1.7	1.46	76	78	86	RES	
4	PONNUSAMY	40	M	10	Y	N	N	N	Y	Y	N	N	11	65	-	+	3.98	Y	Y	N	N	Y	N	Y	N	Y	N	N	N	N	1.52	1.32	57	65	87	RES	
5	RATINAM	59	F	5	Y	N	Y	N	N	Y	N	N	10	55	+	-	4.23	Y	N	Y	N	Y	N	N	N	N	N	Y	N	Y	2.74	2.34	92	89	85	NOR	
6	BALAKRISHNAN	55	M	7	Y	N	N	N	Y	N	Y	N	10	115	+	+	6.33	N	N	N	N	N	Y	N	N	N	N	N	N	N	1.31	1.12	67	69	86	RES	
7	JANAKI	38	F	4	N	N	Y	N	N	N	N	N	9.8	50	+	+	5.33	N	N	N	N	N	N	Y	N	N	N	Y	N	Y	1.86	1.64	95	101	88	NOR	
8	NAZIMA BEGAM	35	F	11	Y	N	N	N	N	N	N	Y	11	52	+	+	5.3	Y	Y	N	N	Y	N	Y	N	Y	N	N	N	N	1.42	1.23	72	76	86	RES	
9	RAJAMMAL	35	F	15	N	N	Y	N	Y	N	N	N	8.2	135	+	+	5.86	N	N	N	N	Y	N	N	Y	N	N	N	Y	N	1.86	1.62	83	91	87	NOR	
10	SARASWATHY	32	F	10	N	N	N	N	N	N	Y	N	8.8	90	+	+	4.53	N	N	N	N	Y	N	Y	N	N	Y	N	N	N	1.33	1.24	59	70	93	RES	
11	VIJAYALAKSHMI	57	F	5	Y	Y	Y	N	N	Y	Y	N	12	32	+	+	4.75	Y	N	Y	N	Y	N	Y	Y	N	Y	N	N	N	1.82	1.48	82	76	81	NOR	
12	KADAMBAN	62	M	26	N	N	Y	N	Y	N	N	Y	12	36	+	-	5.12	N	N	N	N	Y	Y	N	N	N	N	Y	N	N	1.54	1.51	64	76	98	RES	
13	RAJESWARI	48	F	22	Y	N	N	N	Y	Y	N	N	11	22	+	+	4.92	N	N	N	N	N	N	N	N	Y	Y	N	N	Y	2.45	2.24	85	97	91	NOR	
14	POONGODI	44	F	7	N	N	N	N	N	N	Y	N	8.6	35	+	+	5.38	N	N	N	N	Y	N	Y	N	Y	N	N	N	N	1.96	1.84	68	79	94	RES	
15	R.LATHA	39	F	6	N	N	Y	Y	N	Y	Y	N	13	50	+	+	4.93	Y	Y	N	N	Y	Y	N	N	N	N	N	N	N	2.12	1.68	84	86	80	NOR	
16	RAJA	46	M	6	Y	N	N	N	N	N	N	Y	12	44	+	+	5.12	Y	Y	N	N	Y	Y	N	N	N	N	N	Y	N	1.49	1.34	66	71	90	RES	
17	ESWARI	47	F	15	N	N	Y	N	Y	Y	Y	N	8.8	60	+	+	5.55	Y	N	Y	N	N	N	N	N	Y	N	N	Y	N	1.98	1.68	88	86	85	NOR	
18	SELVARAJ	52	M	8	N	N	Y	N	N	N	N	Y	11	38	-	+	4.12	N	N	N	N	N	N	N	N	Y	N	Y	N	N	2.45	2.12	86	83	87	NOR	
19	RAJAMMAL	50	F	16	N	N	Y	N	Y	Y	Y	N	9.8	32	+	+	5.68	Y	N	Y	N	Y	N	Y	N	N	N	N	N	Y	1.54	1.34	65	68	87	RES	
20	NOORJAHAN	36	F	7	Y	N	N	N	N	N	N	Y	9.8	40	+	+	5.1	Y	N	N	Y	N	N	N	N	N	N	N	Y	Y	1.68	1.48	77	79	88	RES	
21	KANNAMMAL	56	F	6	Y	N	Y	y	Y	N	N	N	10	54	+	-	5.97	Y	N	Y	N	Y	Y	N	N	N	N	Y	N	N	1.59	1.32	80	74	83	NOR	
22	SUNDARAM	43	M	11	N	N	Y	N	N	Y	N	N	9.6	60	+	+	6.34	N	N	N	N	N	N	N	N	N	Y	Y	Y	N	1.72	1.56	74	83	91	RES	
23	PERIMBAM	53	F	5	N	N	N	N	Y	N	N	N	11	130	+	+	6.11	Y	Y	N	N	Y	N	N	N	Y	N	N	N	Y	0.98	0.87	49	53	89	RES	
24	AROGYAM	40	M	4	N	N	Y	N	N	N	N	Y	9.6	25	+	+	4.79	Y	Y	N	N	Y	N	N	N	N	Y	N	N	N	2.43	2.12	96	96	87	NOR	

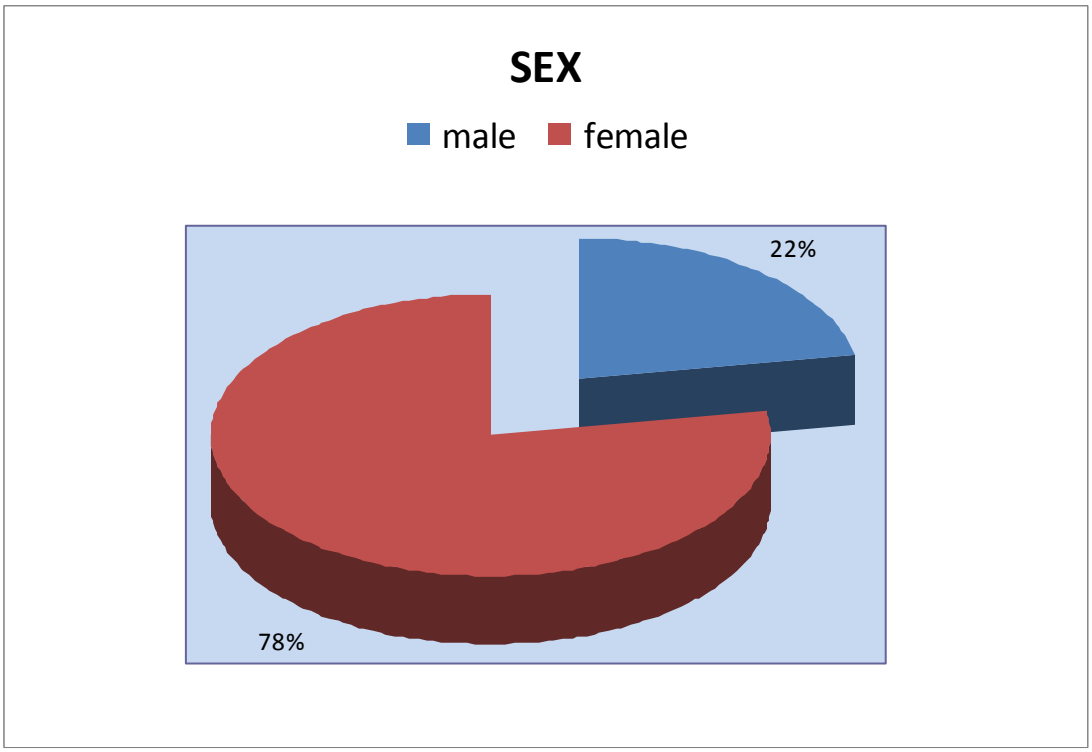
25	PARAMESWARI	40	F	6	N	N	N	N	Y	N	Y	N	9.2	26	+	+	4.98	Y	N	Y	N	N	N	Y	Y	N	Y	N	N	Y	1.74	1.12	91	63	64	OBS	
26	BALARAMAN	51	M	25	Y	N	Y	y	N	Y	Y	N	12	30	+	-	4.21	N	N	N	N	Y	N	Y	N	Y	N	Y	N	N	1.98	1.86	77	79	94	RES	
27	NEETHI THAI	60	F	28	Y	N	Y	N	N	N	Y	N	10	75	+	+	6.36	Y	Y	N	N	Y	N	N	Y	N	Y	N	N	N	1.58	0.98	78	55	62	OBS	
28	ATHIJAYALAKSM	54	F	7	N	N	Y	N	Y	N	Y	N	9	40	+	+	3.1	N	N	N	N	Y	Y	N	N	N	N	Y	N	N	1.63	1.42	57	62	88	RES	
29	RAMUTHAI	62	F	7	N	N	N	N	N	N	Y	N	8.6	60	-	+	5.66	Y	Y	N	Y	Y	Y	N	N	N	N	N	Y	N	1.82	1.76	69	81	97	RES	
30	ANUSIYA	45	F	6	Y	Y	Y	N	N	Y	Y	N	10	120	-	+	4.65	N	N	N	N	Y	N	N	N	N	Y	N	N	N	2.21	2.02	76	80	91	RES	
31	SHANTHI	30	F	7	N	N	Y	N	Y	Y	Y	N	9	48	+	+	4.71	Y	N	Y	N	Y	Y	Y	N	N	N	Y	N	Y	1.56	1.42	70	76	91	RES	
32	FATHIMA	57	F	7	N	N	Y	N	N	N	N	N	9.6	42	+	-	4.1	N	N	N	N	N	N	N	N	N	N	N	Y	Y	2.34	1.87	82	84	80	NOR	
33	ANGAMMAL	65	F	8	N	N	y	N	N	Y	N	Y	10	40	-	+	4.8	Y	N	Y	N	N	N	N	N	N	N	N	N	N	1.98	1.56	85	84	79	NOR	
34	SELVI	47	F	3	N	N	Y	N	N	N	N	N	9.8	45	+	-	5.13	Y	Y	N	N	N	N	N	N	N	N	N	N	N	1.98	1.67	85	80	84	NOR	
35	MURUGAN	39	M	4	Y	N	N	N	N	N	N	Y	12	38	-	+	4.8	N	N	N	N	N	N	N	N	N	N	N	N	N	1.86	1.68	93	103	90	NOR	
36	VIJAYA	43	F	12	N	N	Y	N	N	N	N	N	8.6	70	+	+	6.12	N	N	N	N	N	N	N	N	N	N	N	N	N	1.54	1.41	72	80	92	RES	
37	LALITHA	55	F	7	Y	Y	Y	N	N	N	N	Y	9.6	68	+	-	4.8	Y	Y	N	N	N	N	N	N	N	N	N	N	N	2.42	2.12	90	91	87	NOR	
38	GURULAKSHMI	38	F	5	N	N	Y	N	N	N	Y	N	8.8	40	+	+	3.1	N	N	N	N	N	N	N	N	N	N	N	N	N	2.42	2.12	93	91	88	NOR	
39	JAYA	50	F	6	N	N	Y	N	N	Y	N	N	8.6	130	-	+	4.78	Y	Y	N	N	N	N	N	N	N	N	N	N	N	2.12	1.64	86	83	77	NOR	
40	MANJULA	31	F	3	Y	N	N	y	N	N	N	N	8.8	30	-	-	5.12	Y	Y	N	N	N	N	N	N	N	N	N	N	N	1.97	1.68	88	82	85	NOR	
41	PANDIAN	46	M	7	Y	N	Y	N	Y	N	N	Y	12	54	+	+	5.5	N	N	N	N	N	N	N	N	N	N	N	N	N	1.84	1.68	71	82	91	RES	
42	THENMOZHI	49	F	4	Y	N	N	N	N	N	Y	N	9.8	50	-	+	2.9	Y	N	Y	N	N	N	N	N	N	N	N	N	N	2.2	1.76	89	89	80	NOR	
43	KUMUTHA	52	F	8	N	N	Y	N	N	N	N	N	10	44	+	+	4.2	Y	Y	N	N	N	N	N	N	N	N	N	N	N	1.22	1.12	74	78	92	RES	
44	SUPPU	43	F	3	N	N	Y	y	N	N	N	N	11	50	+	+	5.67	N	N	N	N	N	N	N	N	N	N	N	N	N	2.21	1.78	96	92	81	NOR	
45	RAJAMANI	56	F	20	N	N	Y	N	N	Y	N	N	9.8	36	-	+	6.24	N	N	N	N	N	N	N	N	N	N	N	N	N	1.34	1.21	68	75	90	RES	

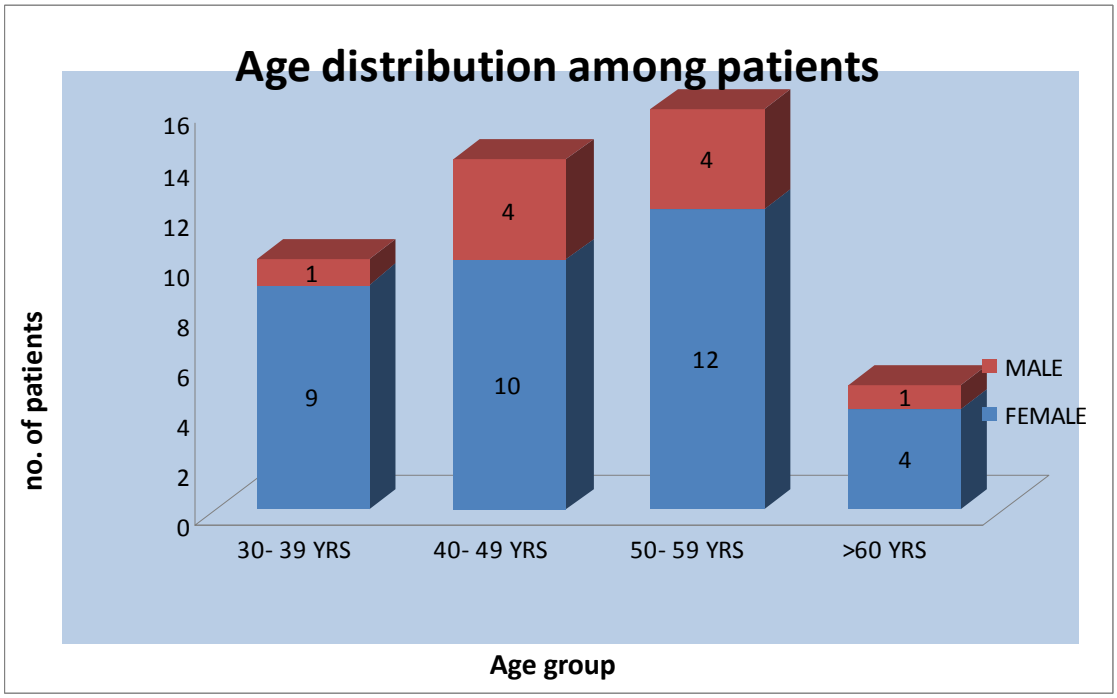
KEY TO MASTER CHART

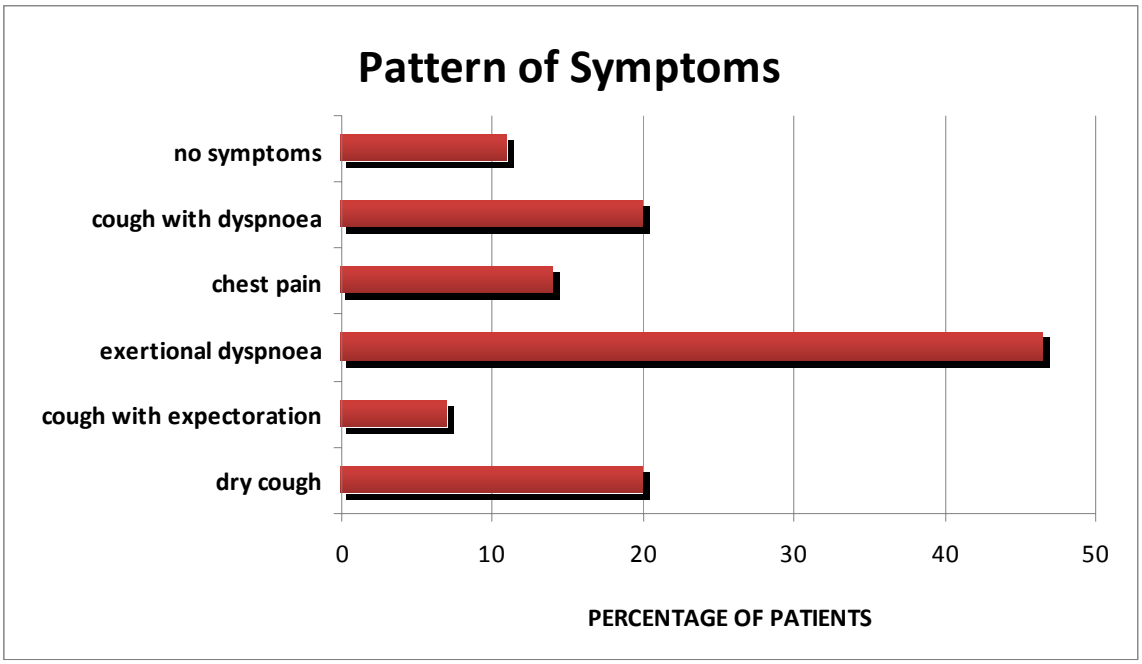
M - MALE F - FEMALE + - POSITIVE - NEGATIVE

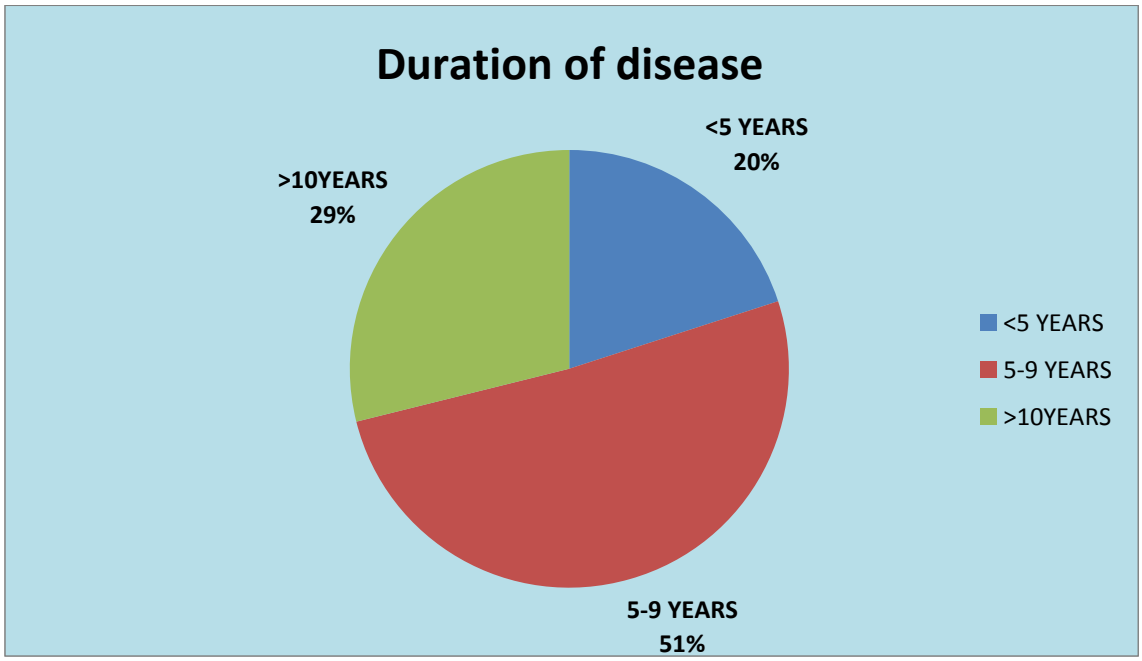
Y - PRESENT N - ABSENT RES - RESTRICTIVE OBS - OBSTRUCTIVE

NOR - NORMAL

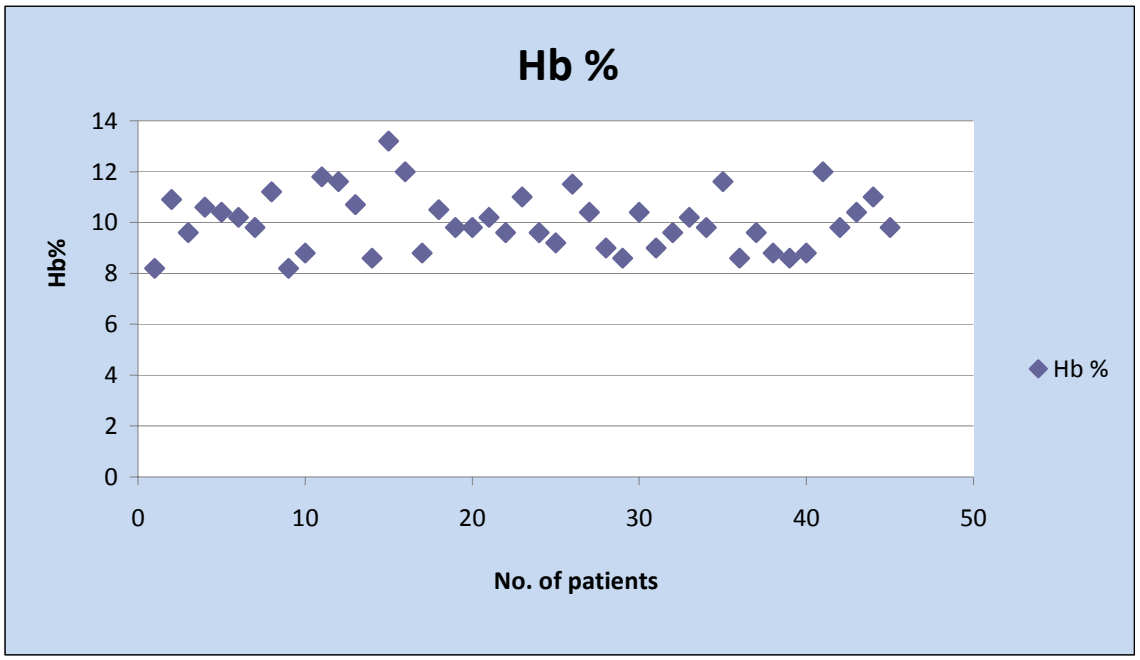

SEX
male
female
22%
78%

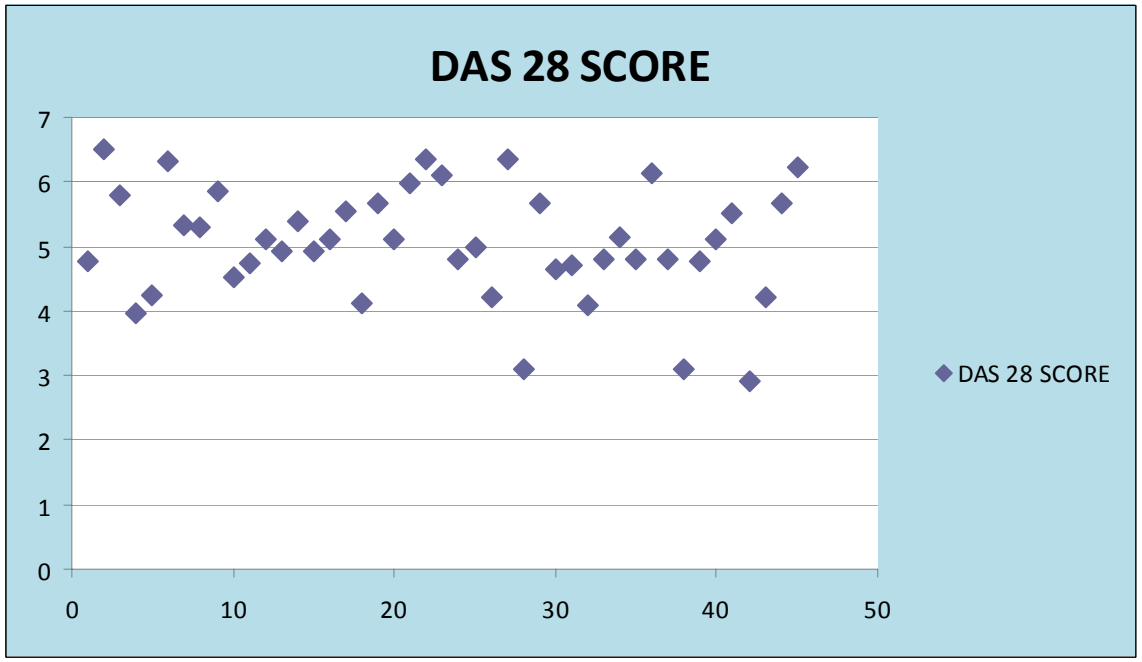

Age distribution among patients
16
14
12
10
8
6
4
2
0
1
9
4
10
4
12
1
4
MALE
FEMALE
30- 39 YRS
40- 49 YRS
50- 59 YRS
>60 YRS
no. of patients
Age group

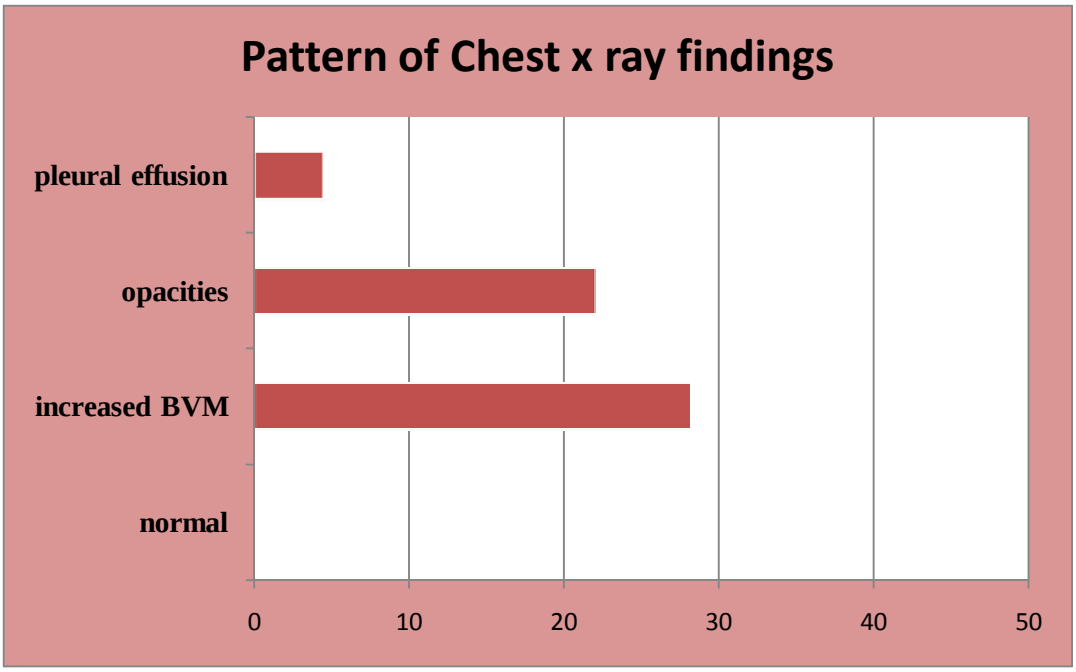

Pattern of Symptoms
no symptoms
cough with dyspnoea
chest pain
exertional dyspnoea
cough with expectoration
dry cough
0
10
20
30
40
50
PERCENTAGE OF PATIENTS

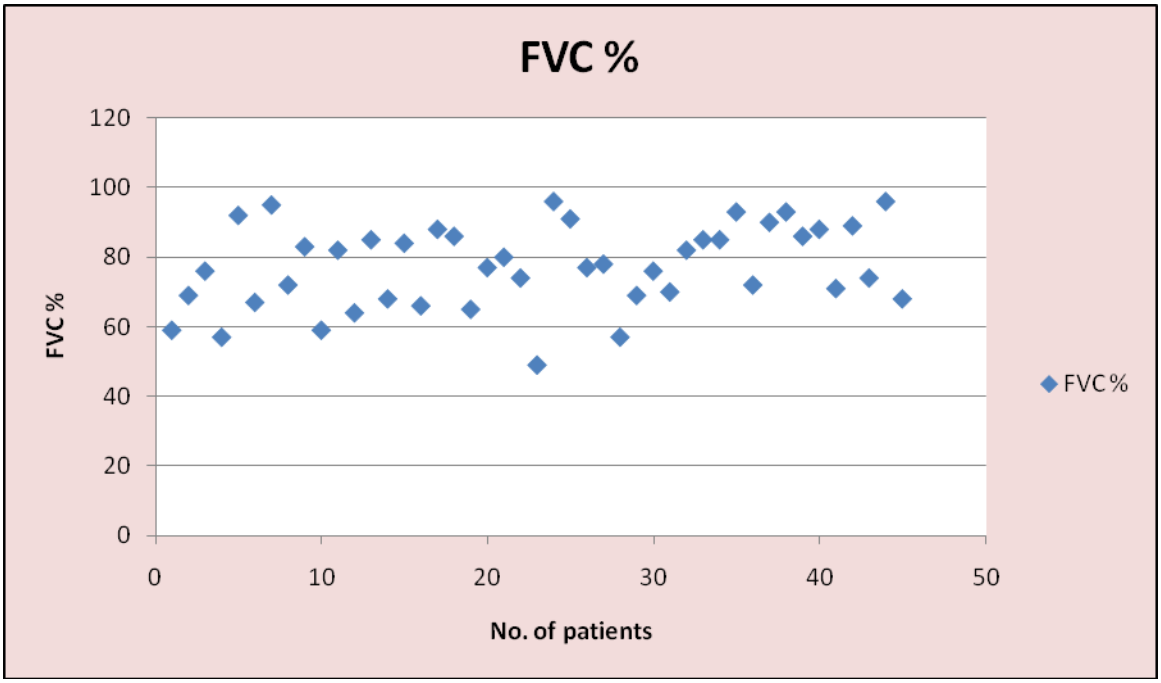

Duration of disease
<5 YEARS
20%
>10YEARS
29%
5-9 YEARS
51%
<5 YEARS
5-9 YEARS
>10YEARS

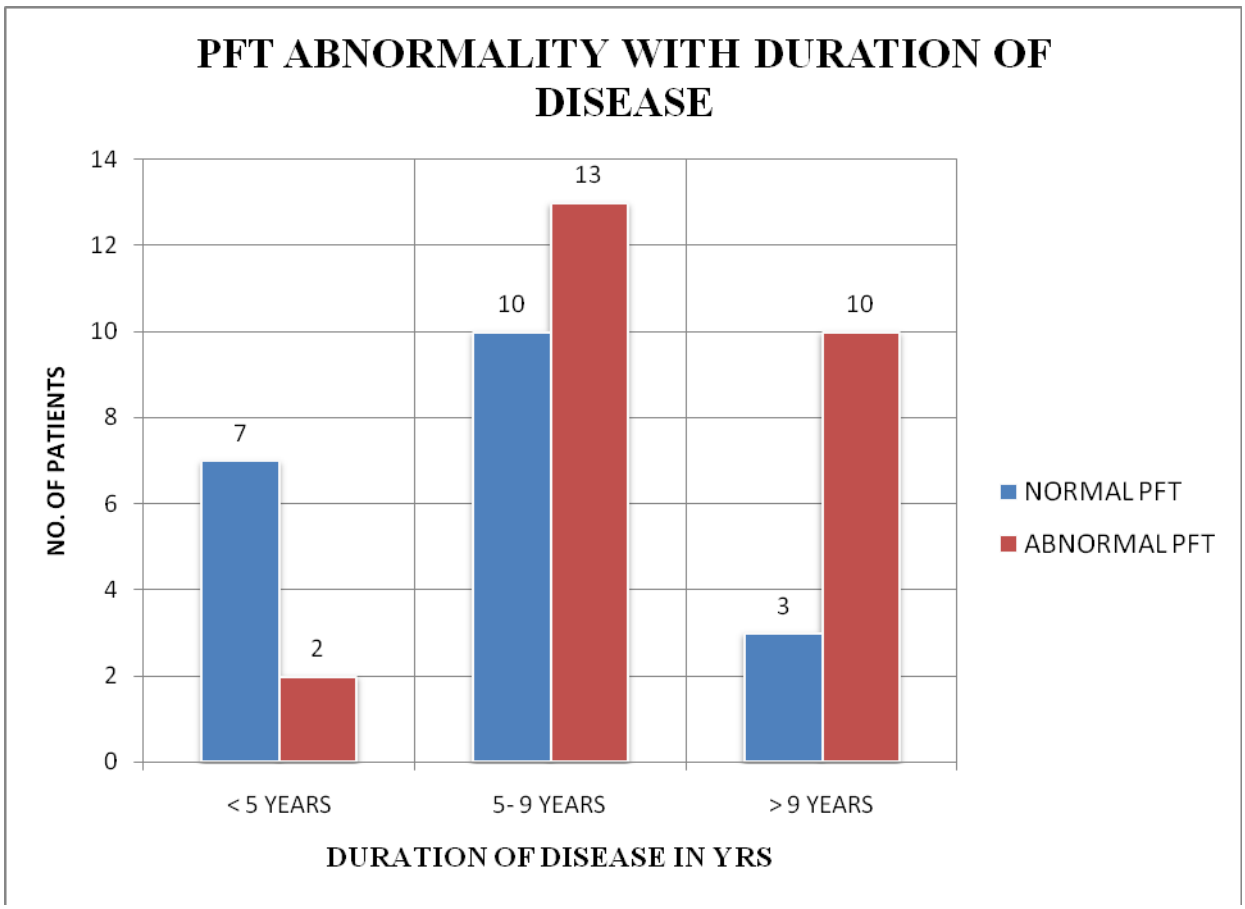
DISTRIBUTION OF Hb AND DAS 28 AMONG CASES:

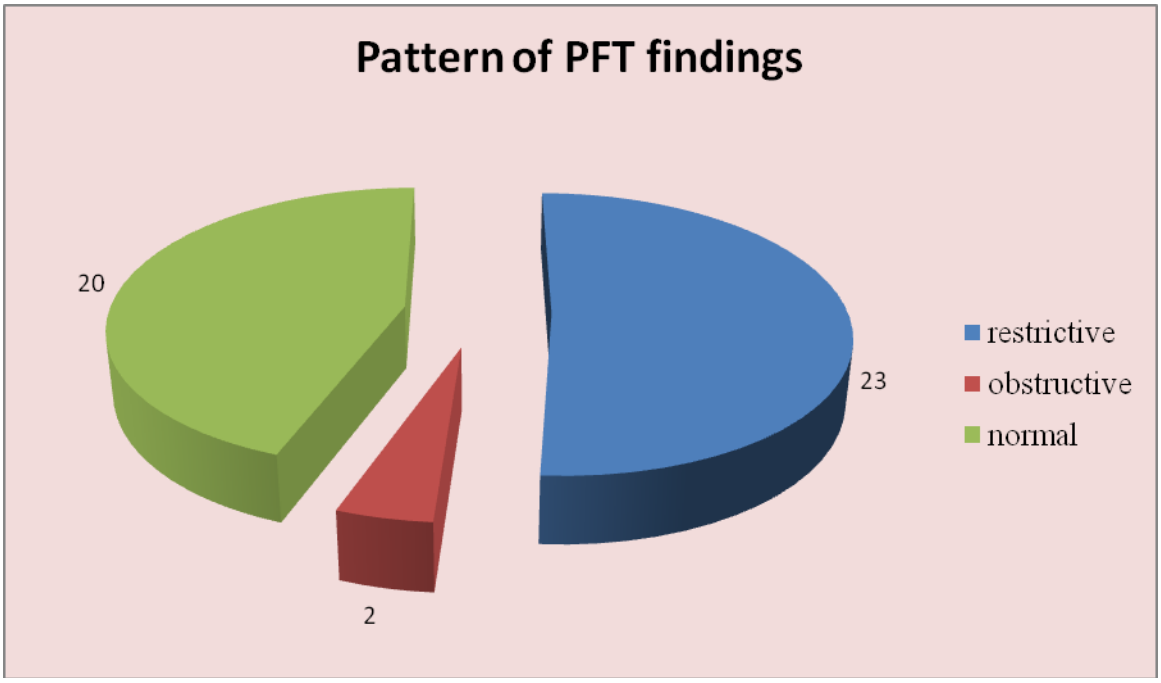


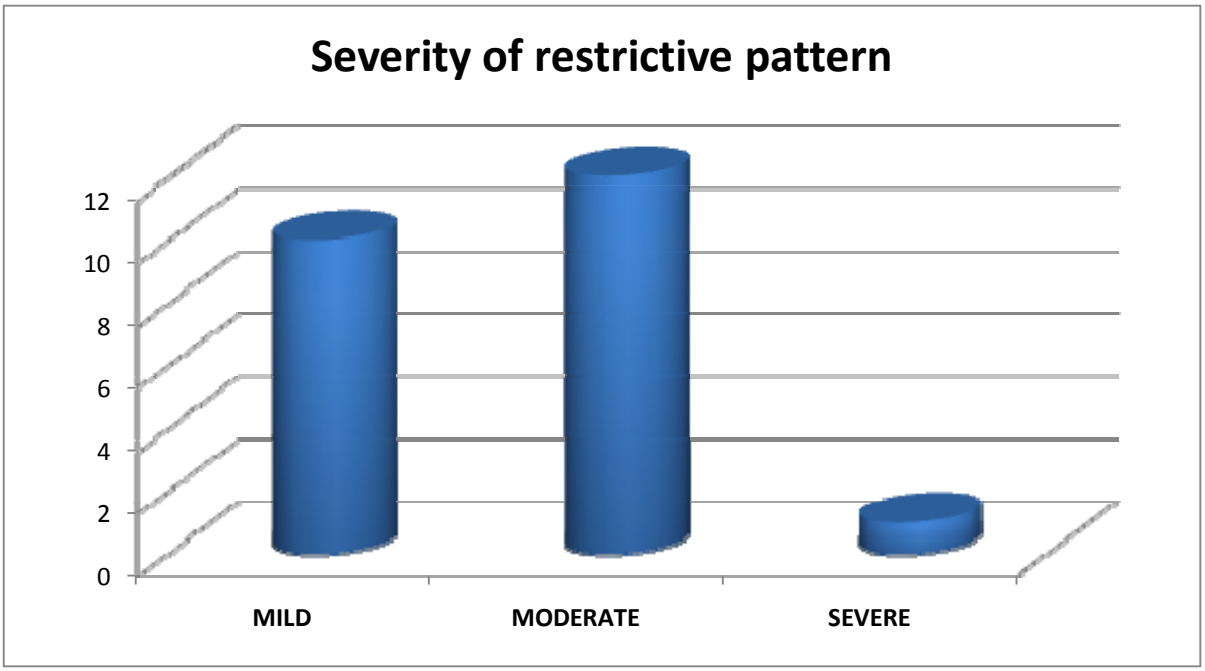


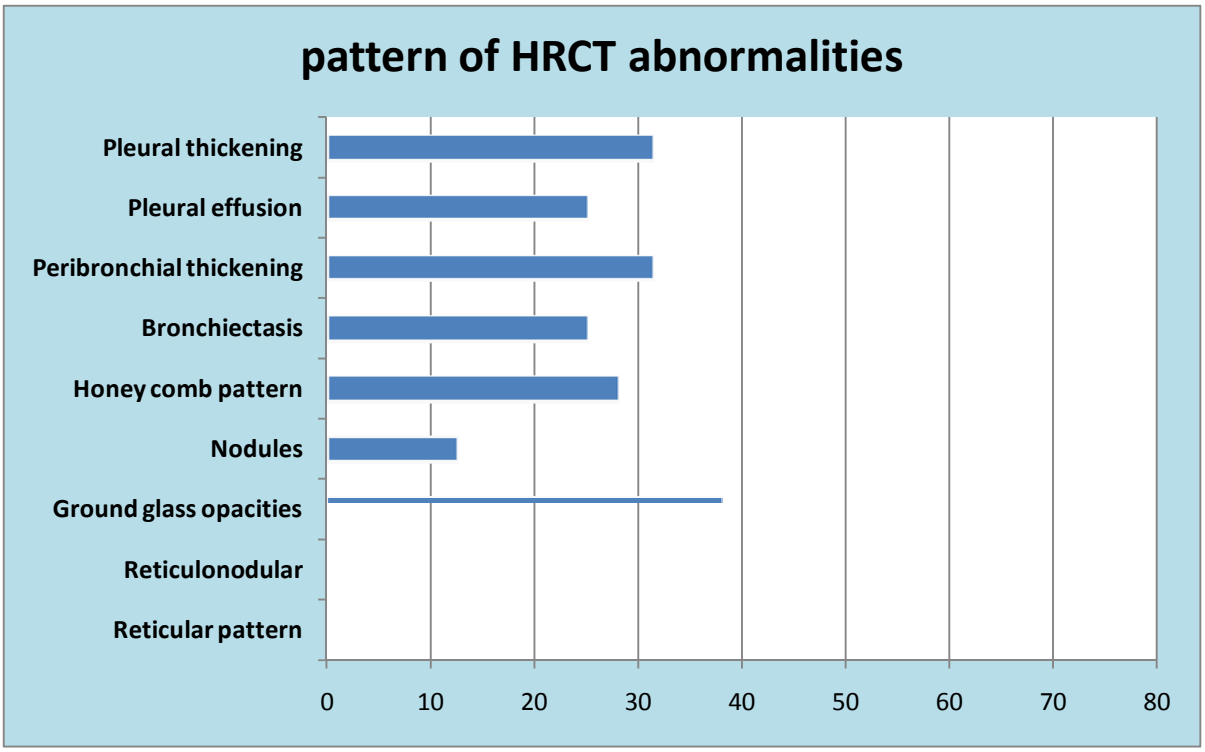

Pattern of Chest x ray findings
pleural effusion
opacities
increased BVM
normal
0
10
20
30
40
50

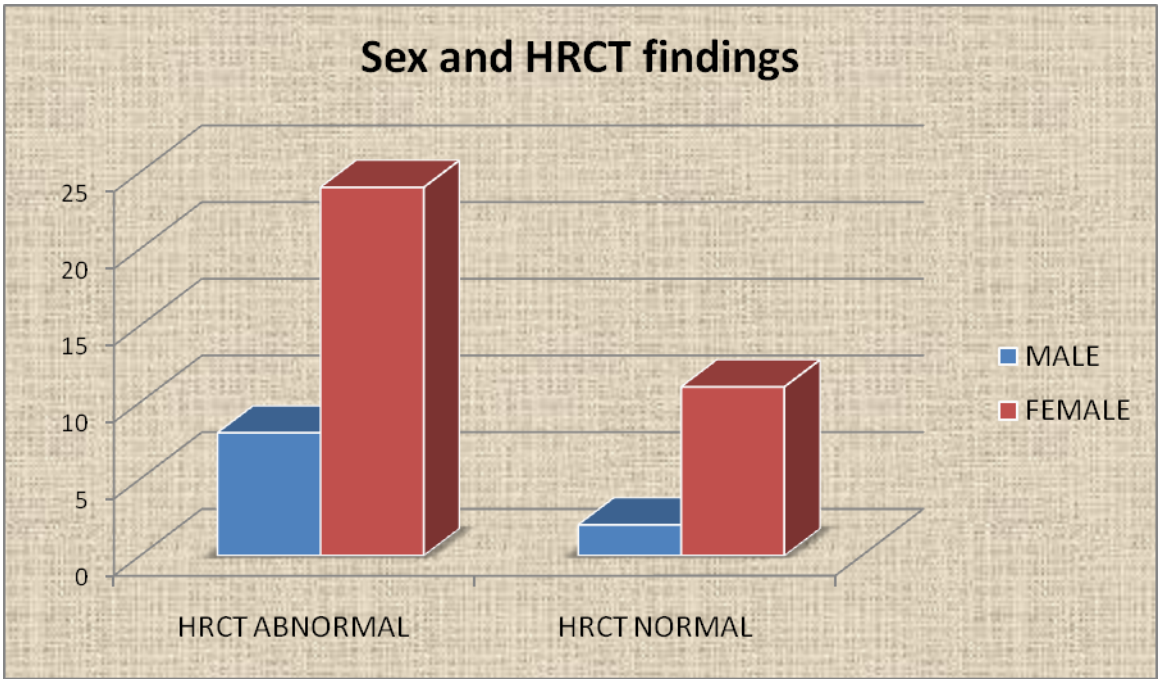

FVC %
120
100
80
60
40
20
0
FVC %
0
10
20
30
40
50
No. of patients
FVC %

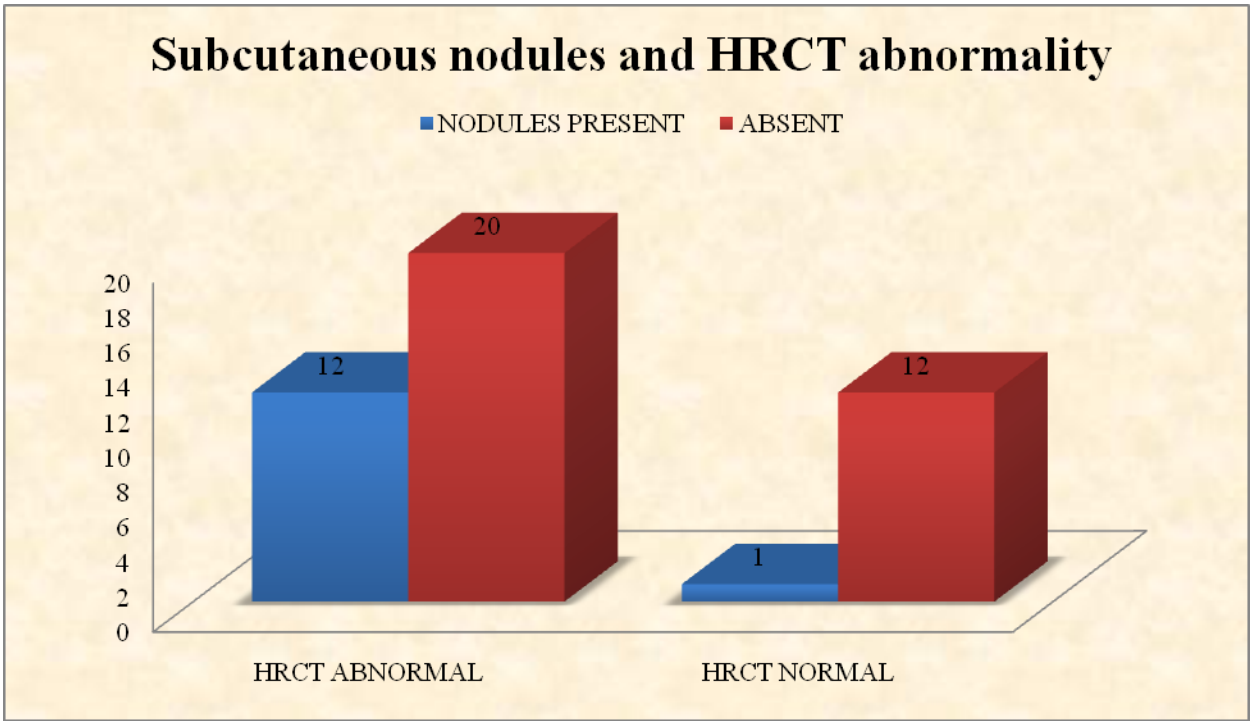

PFT ABNORMALITY WITH DURATION OF DISEASE
14
12
10
8
6
4
2
0
NO. OF PATIENTS
7
2
10
13
3
10
< 5 YEARS
5- 9 YEARS
> 9 YEARS
DURATION OF DISEASE IN YRS
NORMAL PFT
ABNORMAL PFT

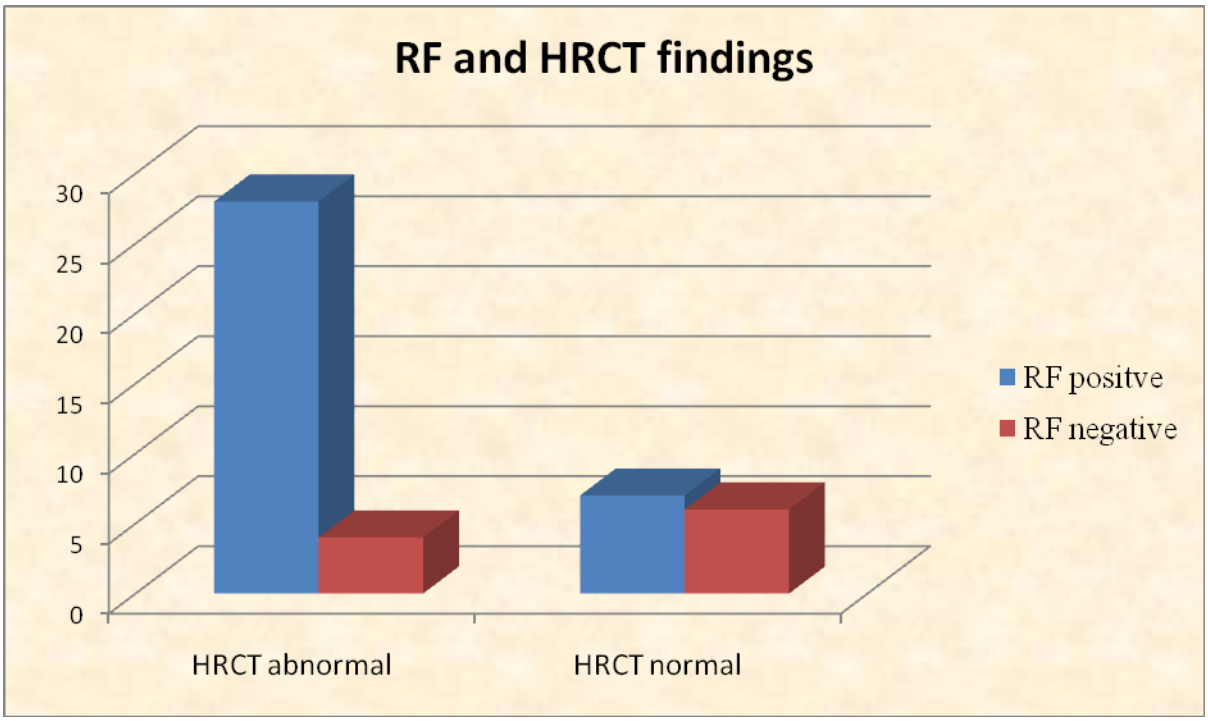

Pattern of PFT findings
20
2
23
restrictive
obstructive
normal

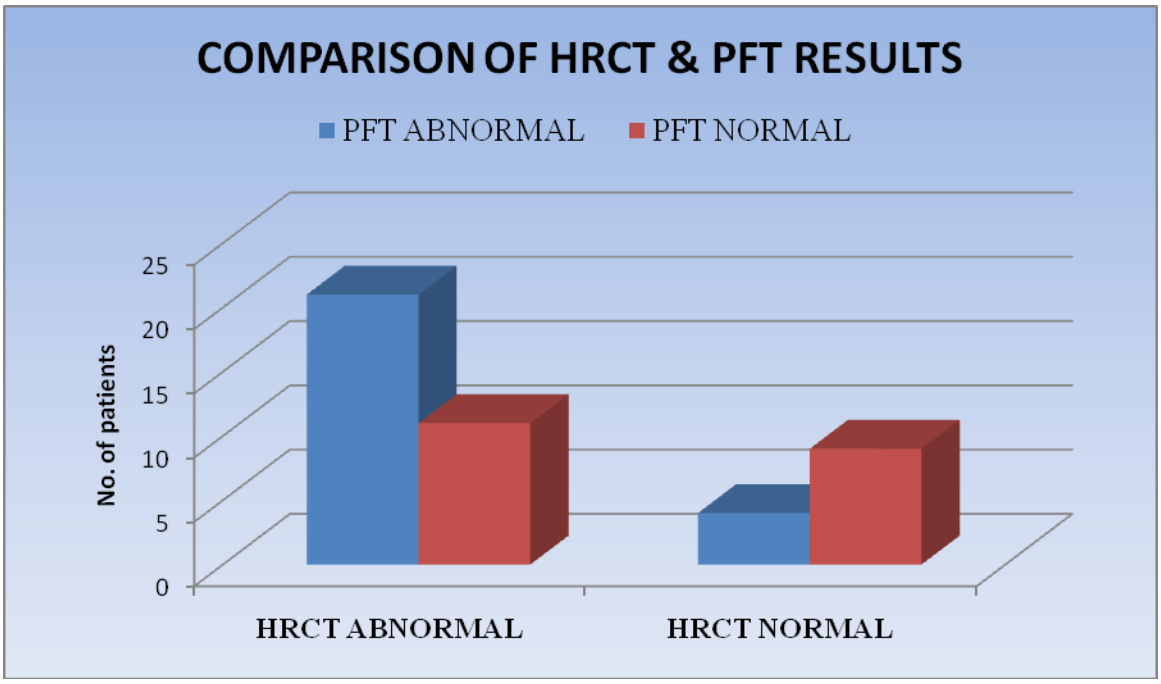

Severity of restrictive pattern
12
10
8
6
4
2
0
MILD
MODERATE
SEVERE

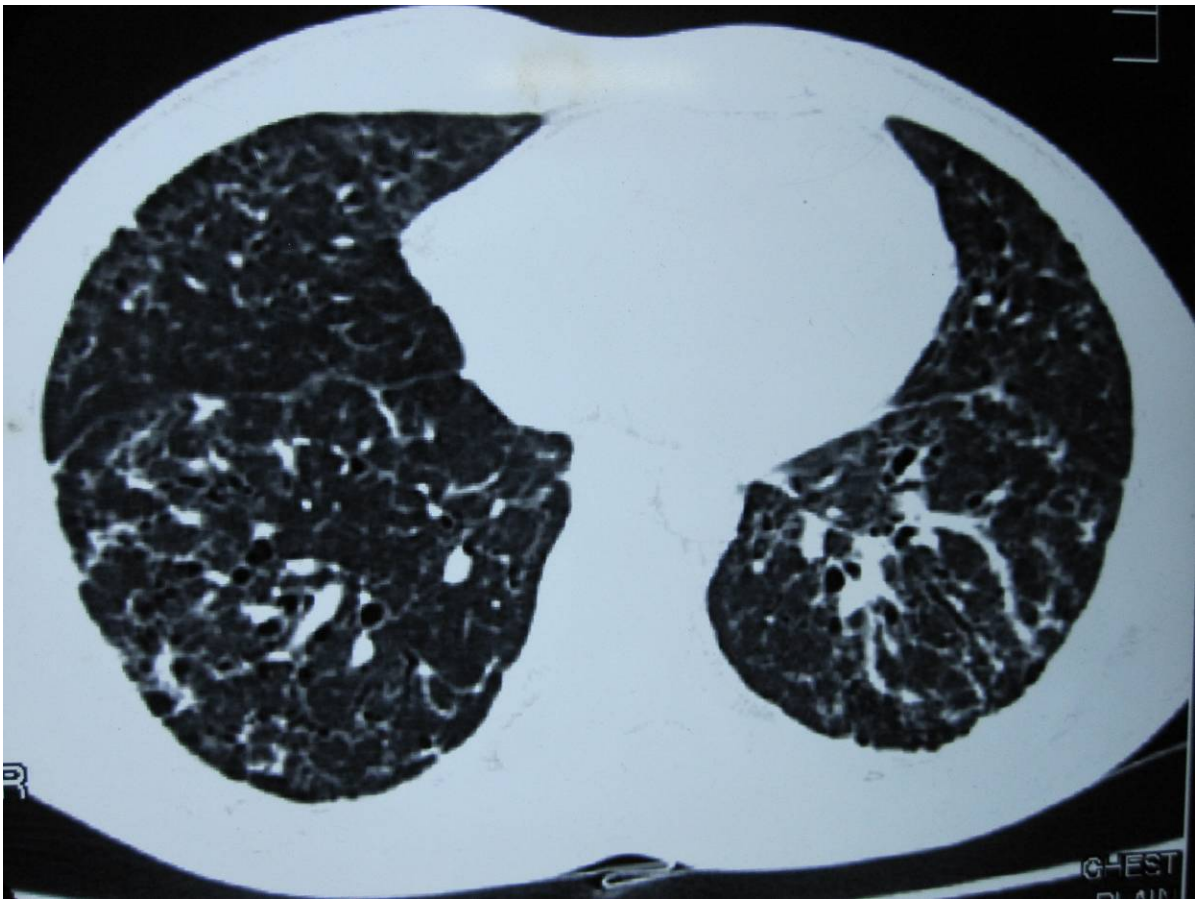

pattern of HRCT abnormalities
Pleural thickening
Pleural effusion
Peribronchial thickening
Bronchiectasis
Honey comb pattern
Nodules
Ground glass opacities
Reticulonodular
Reticular pattern
0
10
20
30
40
50
60
70
80

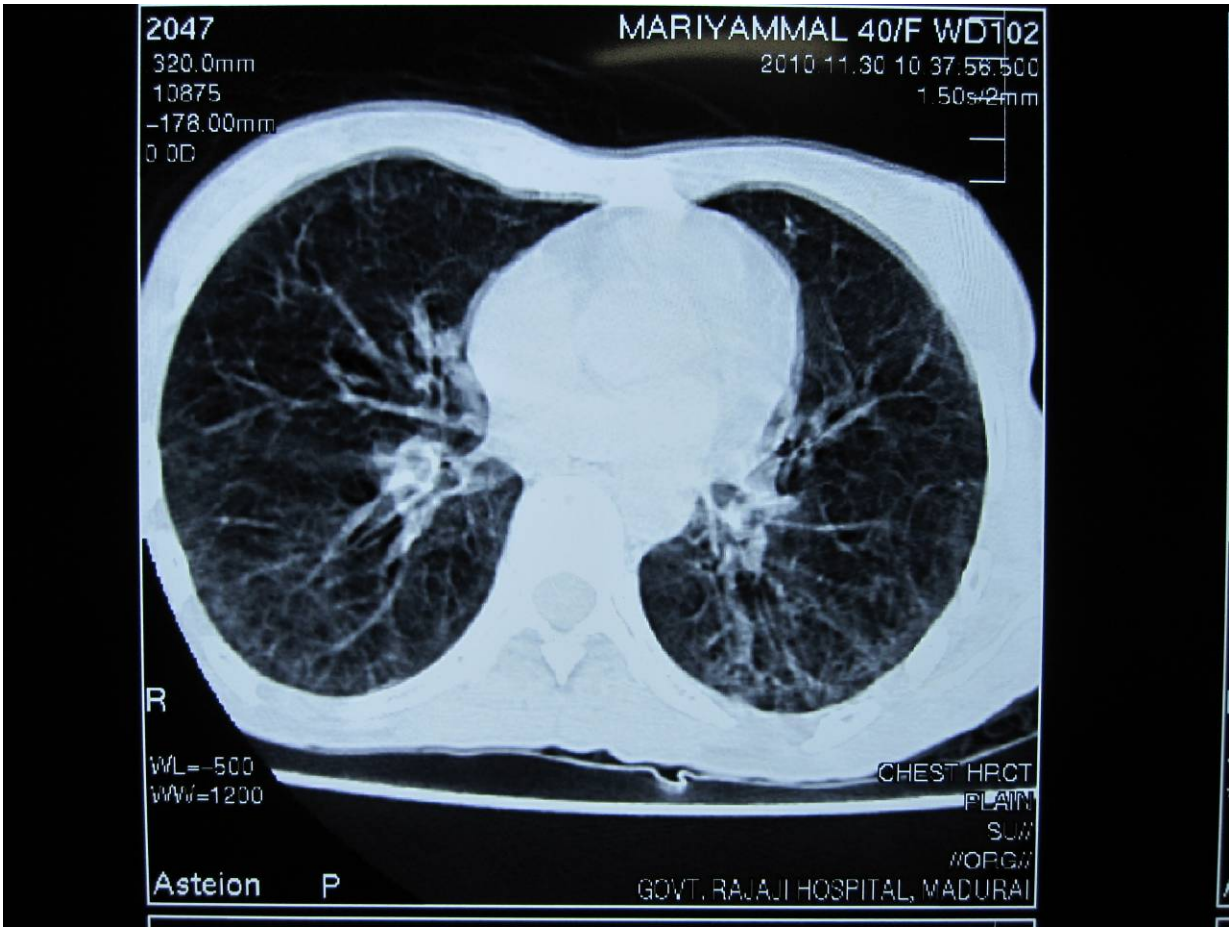

Sex and HRCT findings
25
20
15
10
5
0
HRCT ABNORMAL
HRCT NORMAL
MALE
FEMALE


Subcutaneous nodules and HRCT abnormality
NODULES PRESENT
ABSENT
20
18
16
14
12
10
8
6
4
2
0
12
20
1
12
HRCT ABNORMAL
HRCT NORMAL


RF and HRCT findings
30
25
20
15
10
5
0
HRCT abnormal
HRCT normal
RF positve
RF negative


COMPARISON OF HRCT & PFT RESULTS
PFT ABNORMAL
PFT NORMAL
No. of patients
25
20
15
10
5
0
HRCT ABNORMAL
HRCT NORMAL


R
G-EST


2047
MARIYAMMAL 40/F WD102
320.0mm
10875
-178.00mm
0.0D
1.50s+2mm
R
WL=-500
WW=1200
CHEST HR.CT
PLAIN
SU//
//OP:G//
Asteion
P
GOVT. RAJAJI HOSPITAL, MADURAI